Protein-altering variants associated with body mass index implicate pathways that control energy intake and expenditure in obesity

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Protein-altering variants associated with body mass index implicate pathways that control energy intake and expenditure underpinning obesity

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SUPPLEMENTARY NOTE

1. COMMON CODING VARIANTS ASSOCIATED WITH BMI

The main focus of our study was the analysis of the 215,917 rare and low frequency (R/LF) coding variants, which are more likely to disrupt protein function[1,2]. However, besides R/LF coding variants, the ExomeChip also carries 13,786 common coding SNVs, which were also tested for association with BMI as part of the study.

We identified 41 novel loci that showed association with BMI (AWS: $P<2.0x10^{-7}$), independent from any previously identified loci (**Supplementary Table 4, Supplementary Figure 4**). The reasons why these 41 novel loci has not been reported by previous large-scale GWAS before are; the sample size of the current study is more than twice as large as the most recent GWAS[3],thus providing greater statistical power for discovery, and/or SNPs may not have been tested in previous GWAS efforts because they were not available in HapMap, and thus not imputed, SNPs did not pass quality control, or are located on the X-chromosome, which has so far not been considered in GWAS.

We also identified common variants that clustered in 51 loci that had been identified before (<1Mb previous GWAS lead SNP) in large-scale GWAS efforts of adiposity traits (**Supplementary Table 4, Supplementary Figure 4**). Using conditional analyses (**Online Methods**), we were able to show that 38 of these 51 loci represent the same locus as the one identified before and one represents an independent secondary signal in the previously established locus. For the remaining 12 loci, we were not able to confirm whether the association represented secondary or the same signal within the established locus because the original SNP (or proxy) was not available on the ExomeChip to perform conditional analyses (**Supplementary Table 4, Supplementary Figure 4**).

Effect sizes of the 41 novel loci are smaller (on average 0.014 SD/allele, [range: 0.010 – 0.024 SD/allele]) than those of the 37 previously established loci (average 0.021 SD/allele, [range: 0.010 – 0.050 SD/allele]) (**Supplementary Figure 5**). This difference is likely due to the increased sample size (N>700,000), and thus power, of our meta-analyses, compared to sample size of

previous GWAS efforts (N up to 340,000), allowing the identification of loci with smaller effects. Signals in established loci, for which conditional analyses could not convincingly determine whether it was a secondary observation, have effect sizes in between the novel and established loci (average 0.016 SD/allele, [range: 0.010 – 0.030 SD/allele]). The explained variance of the 41 novel loci ranges between 0.004% and 0.02%, and add up to a combined explained variance of 0.394%, as compared to the 2.7% of the variance explained by the 97 loci reported in our latest GWAS BMI effort[3].

The novel common coding loci have features similar to those of previously established GWAS loci; i.e. they represent a cluster of variants in high LD with each other that require further fine-mapping efforts to identify the causal genes/variants in the locus. The common coding variants, including those that reached $P<5x10^{-4}$, were included in the EC-DEPICT analyses and results are described in the **Main text**.

2. COMPARISON OF NOVEL COMMON, LOW FREQUENCY AND RARE VARIANTS ACROSS ANCESTRIES

2.1. Low-frequency and rare coding SNVs

We observed no significant heterogeneity in effect sizes across ancestries, accounting for multiple testing across novel SNVs ($P_{threshold} = 9x10^{-4} = 0.05/(14+41)$), which may in part be due to low statistical power in non-European ancestry populations **(Supplementary Table 7, Supplementary Figure 6).** Minor allele frequencies are general consistent across ancestries, with two exceptions. The minor allele of rs7636 (p.Pro477Pro) in *ACHE* is of low frequency in European ancestry populations (4.2%), but much more common in African (24.4%) and Hispanic (9.9%) ancestry populations and, similarly, that of rs12236219 in *ZNF169* is of low frequency in European ancestry populations, but common in all other ancestries studied.

Of interest are the two SNVs (p.His353Asn, p.Pro477Pro) in *ACHE,* which track together nearly perfectly in European ancestry populations (r^2=0.98; *D'*=0.99, MAFs=4.2%), whereas in African ancestry populations they are not correlated (r^2=0.01; *D'*=0.95). In the African ancestry

data, the non-synonymous SNV p.His353Asn is rare (0.60%) and has a similar estimated effect size (0.057 SD/allele, 95% CI [-0.050-0.164], *P*=0.29) to the effect seen in European ancestry individuals (0.034 SD/allele, 95% CI [0.023-0.044]), whereas the synonymous p.Pro477Pro is common (24.4%) and has no detectable effect on BMI (-0.006 SD/allele, *P*=0.56). Even though our sample size was relatively small, an effect of 0.023-0.044 SD/allele, as observed in European ancestry individuals, would have been detectable in our African-ancestry population (MAF=24.4%, N~24,000, power ~80%, at α=0.01). The absence of such association suggests that p.Pro477Pro may not be driving the association at this locus and that p.His353Asn (or potentially a variant correlated with p.His353Asn, but not with p.Pro477Pro, in African-ancestry populations) is more likely to be the causal variant. This is consistent with functional role of many non-synonymous, as compared to synonymous variants.

2.2. Novel common SNVs

None of the 41 novel commons SNVs showed evidence of heterogeneity across ancestries ($P_{threshold}$ = $9x10^{-4}$). Generally, allele frequencies of the BMI-increasing allele in European ancestry populations were consistent with those of South Asian (r^2 = 0.82) and Hispanic (r^2 = 0.86) ancestry populations, and somewhat lower with African (r^2 = 0.52) and East Asian (r^2 = 0.48) ancestries **(Supplementary Table 7, Supplementary Figure 6)**. Because of the relatively small sample sizes of non-European ancestry populations, statistical power for replication of associations observed in the total sample or European ancestry only meta-analyses was low. Nevertheless, of the 41 SNVs, associations were directionally consistent for 32 SNVs (78%), of which 7 reached nominal significance, in the African ancestry meta-analysis **(Supplementary Table 7, Supplementary Figure 6)**. The directional consistency between European ancestry associations was similar for South Asian (34 SNVs (83%) of which 5 nominally significant) and Hispanic (34 SNVs (83%) of which 3 nominally significant) ancestry populations, and lower for East Asian ancestry populations (61 SNVs (61%) of which 6 nominally significant).

3. GENE SET ENRICHMENT ANALYSIS (EC-DEPICT)

DEPICT is a method for gene set enrichment analysis and gene prioritization of GWAS data[4]. Briefly, 14,462 gene sets from KEGG[5], REACTOME[6], Gene Ontology[7], InWeb[8] (protein-protein networks) and Mouse Phenotype[9] databases were obtained and "reconstituted" using large-scale microarray data, based on the logic of guilt-by-association (genes with similar patterns of expression are more likely to be members of the same gene sets). We have adapted the gene set enrichment functionality of DEPICT for the ExomeChip (EC-DEPICT), with a few alterations: (1) instead of including all genes within a specified amount of linkage disequilibrium to each index SNP, we include only the gene containing the index SNV, (2) we include only nonsynonymous and splicing (coding) SNVs, discarding noncoding associations and (3) we use null ExomeChip data for p-value calculation (rather than null GWAS data). In this supplement, we provide a brief overview of the method and more detailed explanations of each analysis.

3.1. Method

The EC-DEPICT method has been described elsewhere[10]. We generated null ExomeChip data from the Malmö Diet and Cancer (MDC), All New Diabetics in Scania (ANDIS), and Scania Diabetes Registry (SDR) cohorts (a total of 11,899 samples with Swedish ancestry). After generating simulated normally-distributed phenotypes, we conducted 2,200 null ExomeChip association studies, filtering out all variants not present in the BMI association study. The variants in each null study were then sorted by ascending *P*-value and clumped (+/- 1 Mb on each side). Annotations from the CHARGE consortium were used to assign variants to genes (see URLs). For analyses of rare/low-frequency variants, a separate set of backgrounds was created that retained only loci where the index SNV had a minor allele frequency of <5%.

The method for gene set enrichment is as follows. A list of significant input variants from the ExomeChip is obtained (index SNVs for each locus, coding variants only) and filtered to remove variants not present in the null backgrounds or that are not marked as nonsynonymous/splice-site in the CHARGE consortium annotations. Then, we map the variants

to genes. For each gene set, we then calculate a test statistic: the sum of gene set membership z-scores from the reconstituted gene sets[1] for the input genes. We then take 2000 nulls and compute the average (null) test statistic and standard deviation for the given gene set (where the number of top genes we take from each null as "input genes" is matched to the observed number of input genes). A z-score for the gene set is then computed as the observed test statistic minus the null test statistic divided by the null standard deviation, which is converted to a p-value based on the normal distribution. False discovery rates (FDRs) were calculated using an additional 50 null permutations to generate a distribution of null p-values. The FDR was calculated as the average number of null p-values less than a given threshold divided by the number of observed p-values less than that threshold.

Our null data (MDC, ANDIS, and SDR cohorts) was also used for the ExomeChip analysis of height[10]. As in the height analysis, before gene set enrichment analysis of BMI-associated variants, we removed variants absent in this null ExomeChip data. This resulted in exclusion of about 30% of the BMI-associated variants at suggestive of array-wide significance. Most of the excluded variants were in the very rarest allele frequency bins, and mostly reached suggestive rather than array-wide significance. The exclusion of the rarest variants is expected due to the much smaller sample size of the null cohorts relative to the BMI data. To try to include more variants in the analysis, we also generated null ExomeChip data based on the UK Biobank, which resulted in the exclusion of fewer BMI-associated variants (due to the much larger sample size of the UK Biobank data). However, we observed that use of these null data, despite including more of the rarest BMI-associated variants in the gene set enrichment analysis, dampened the signal and resulted in fewer significantly enriched gene sets. This result suggests that 1) the rarest variants are more likely to have a lower true positive rate and/or 2) the heterogeneity of the underlying biology increases with the inclusion of very rare variants.

Although some variants were excluded from the EC-DEPICT analysis, we have included them in the heatmap figures (Figure 2, Supplementary Figure 10). This is because we assume

that if the genes containing those variants have strong predicted membership in gene sets found to be significantly enriched, they are still good candidates for prioritization (and one of the main purposes of the heatmap strategy is to visually prioritize the best candidate genes). In fact, this is arguably even stronger evidence for prioritization of these genes, because they had no opportunity to influence the gene sets that are identified as enriched and, as such, independently support the biology implicated by these gene sets.

We have observed that extreme non-normality of gene set membership z-scores can, in certain situations, cause minor inflation of Type I error. To address this issue, we repeated the original EC-DEPICT analysis with an inverse-normal-transformed version of the reconstituted gene sets, in which every gene set is forced to have a normal z-score distribution for pathway membership. We then compared the rank of each significant gene set in the original results with the rank in the inverse normal transform and flagged "outliers" with respect to the change in rank (> 1.5 * the interquartile range). In visualizing the results with heat maps and in supplementary tables, outlier gene sets were excluded.

3.2. Analyses

We performed four different analyses of the BMI-associated variants. In each case, for each locus, we included the best coding variant, including secondary signals if present. "GWAS-independent" analyses were performed by excluding EC loci conditionally dependent on or <1 Mb away from a known GWAS locus (see below for details). For this purpose, "known loci" consisted of a list of all variants used as input in the original DEPICT analysis in Locke et al.[3] ($P<5x10^{-4}$). This was necessary to confirm true independence from the original DEPICT findings (i.e. gene set enrichment results for EC that come from a completely non-overlapping set of genes relative to the original DEPICT analysis).

The breakdown of included variants is as follows. Array-wide significant variants ($P<2x10^{-7}$) came from the final meta-analysis of Discovery, deCODE, and UK Biobank results across all analysis strata. For these variants ("stringent"), independence from genome-wide significant

GWAS loci was determined by conditional analysis. Additional variants with p-values between $5x10^{-4}$ and $2x10^{-7}$ ("relaxed") were based on Discovery in the all-ancestries sex-combined additive model. For these variants, independence from genome-wide significant GWAS loci was based on a distance of >1 Mb. For both stringent and relaxed variants, independence from marginally significant GWAS loci was also based on a distance of > 1 Mb. All loci were clumped +/- 1 Mb.

For the first analysis, we included all EC loci with $p<5x10^{-4}$. After filtering, this left 244 variants in 242 genes; we discovered 67 gene sets (24 meta-gene sets) at FDR <0.05. After removing inverse normal transform outliers (see description above), that left 62 gene sets (still in 24 meta-gene sets). The second analysis included EC loci with $5x10^{-4}$ "independent" of a known GWAS locus[3] (110 variants in 110 genes after filtering). We found no significant gene sets in this analysis.

The third and fourth analyses included rare and low-frequency (RLF; <5% MAF) variants only. The third analyses included all RLF variants with $P<5x10^{-4}$, representing a total of 50 variants in 50 genes after filtering. We found 512 significant gene sets at FDR <0.05 (107 meta-gene sets). After applying the inverse normal transform filter, this was reduced to 471 significant gene sets in 106 meta-gene sets. Finally, the last analysis included RLF variants with $P<5x10^{-4}$ "independent" of a known GWAS locus[3] (after filtering, 30 variants in 30 genes). This recovered 31 significant gene sets in 12 meta-gene sets at FDR <0.05. After the inverse normal transform, we retained 29 significant gene sets, still in 12 meta-gene sets.

3.3. Affinity propagation clustering

To collapse the most highly correlated gene sets, affinity propagation clustering was performed as described in Marouli et al. (2017)[10]. Briefly, "meta-gene sets" were generated by affinity propagation clustering[3] of all pairs of 14,462 gene sets, using SciKit-Learn.clustering.AffinityPropagation version 0.17[11], with a maximum iteration of 10,000 and a convergence iteration of 1,000. For each meta-gene set, *P*-values were assigned based on the most significant member gene set (considered the "best representative gene set"). In heat maps,

z-scores for meta-gene set membership represent the z-score of the best representative gene set. Heat maps were generated with the ComplexHeatmap package in R[12]. For Online Mendelian Inheritance in Man (OMIM) annotations, a manual curation of obesity-related terms in the OMIM database was performed.

3.4. URLs

CHARGE Consortium ExomeChip annotation file:

http://www.chargeconsortium.com/main/exomechip/

EC-DEPICT: https://github.com/RebeccaFine/obesity-ec-depict

EC-DEPICT meta-gene sets: https://github.com/RebeccaFine/obesity-ec-depict/blob/master/data/metacluster_labels.txt

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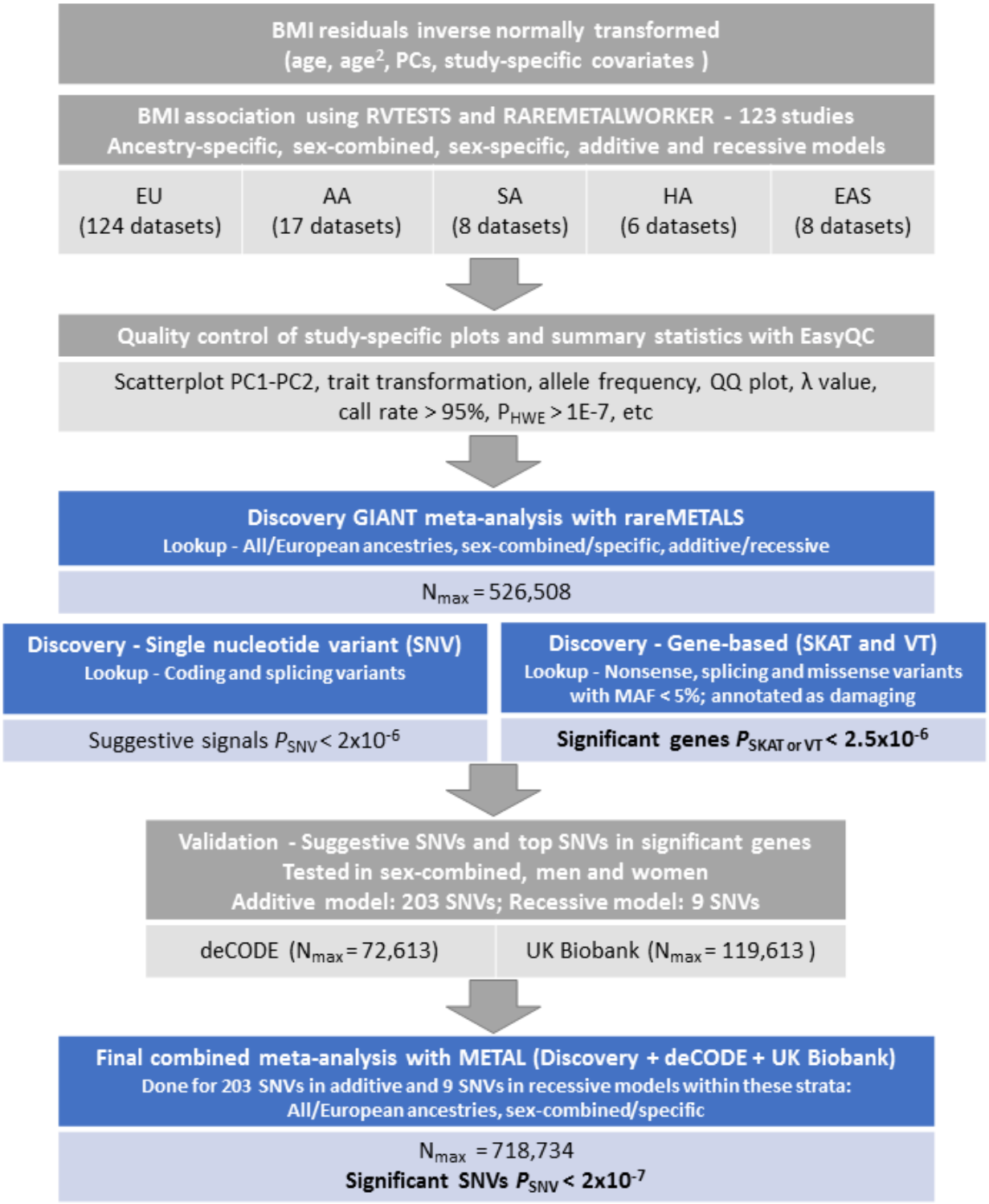
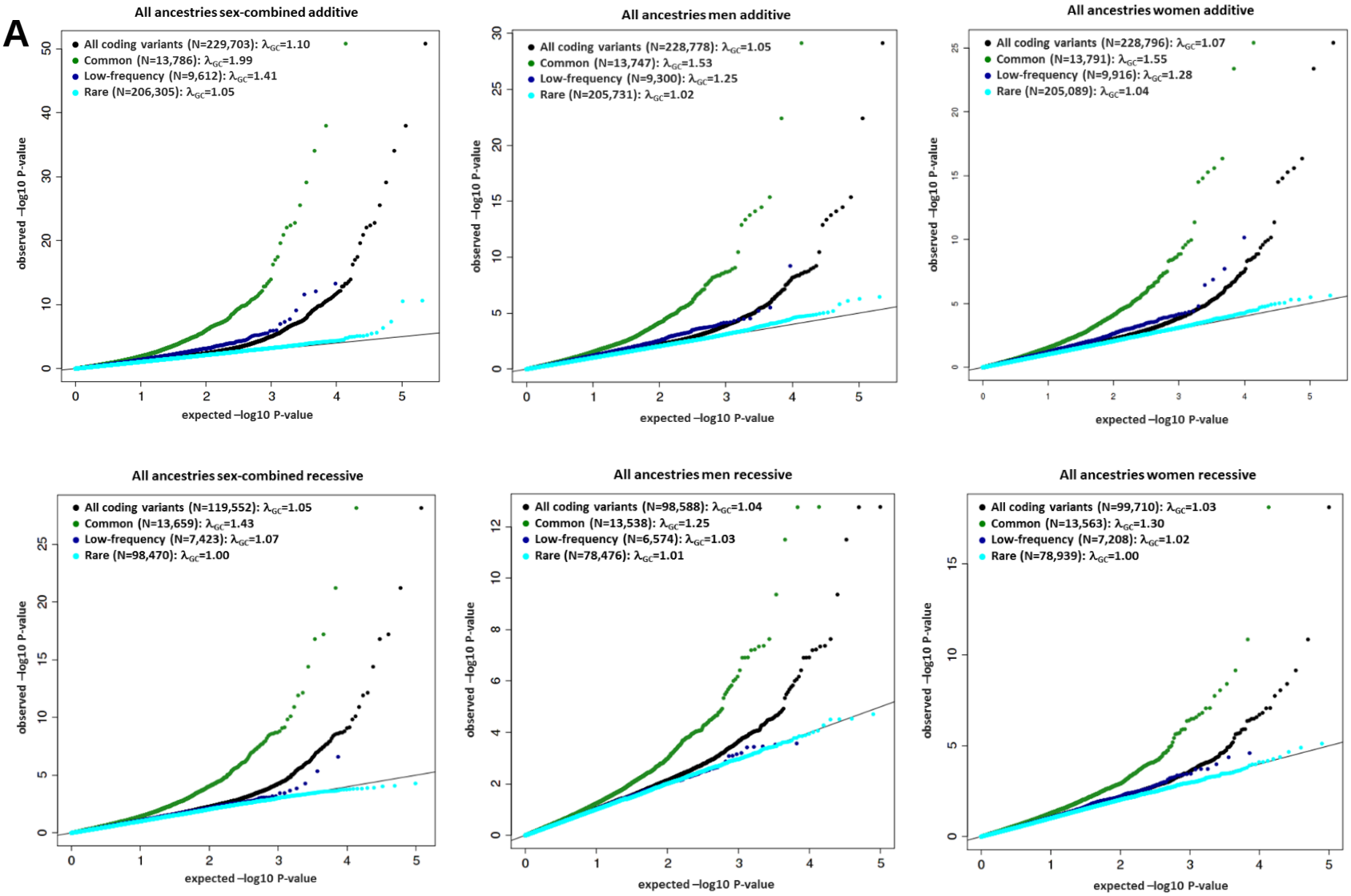
15. Boehnke, M. *et al.* Department of Biostatistics and Center for Statistical Genetics, University of Michigan, Ann Arbor, MI, 48109, USA.
16. Sim, X. Saw Swee Hock School of Public Health, National University Health System, National University of Singapore, Singapore 117549, Singapore

4. SUPPLEMENTARY FIGURES

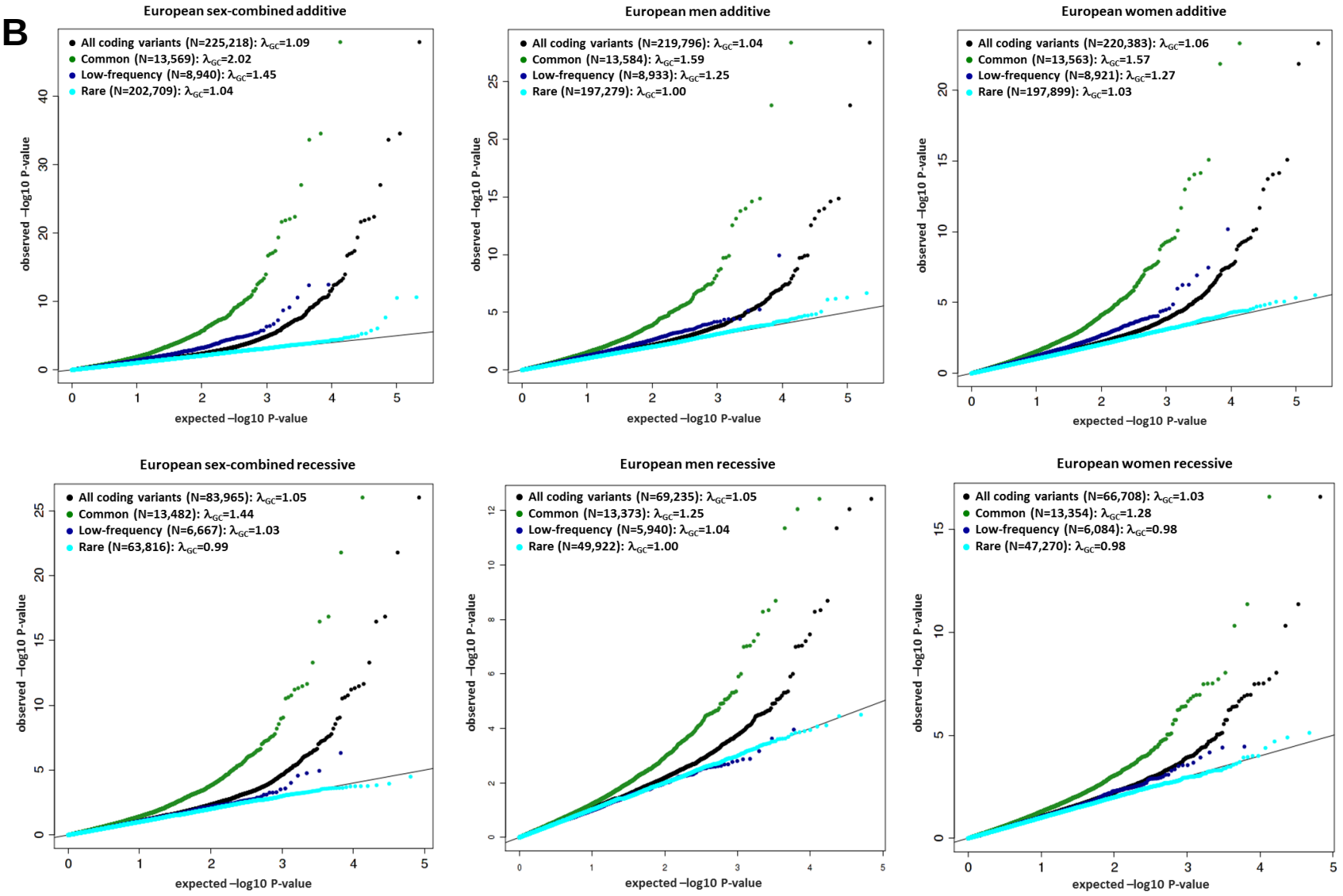
Supplementary Figure 1 | Flowchart of the GIANT ExomeChip BMI study design.

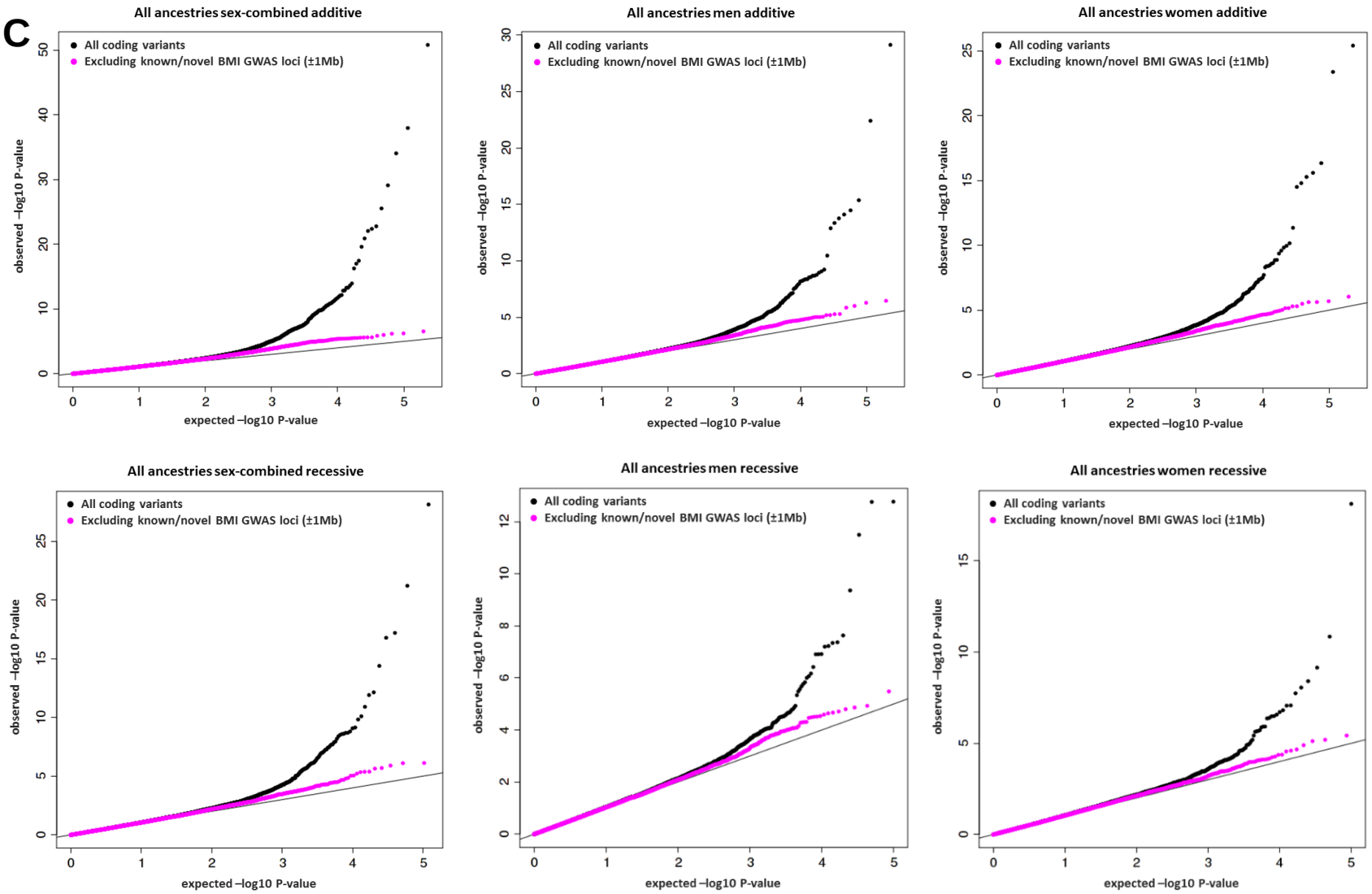


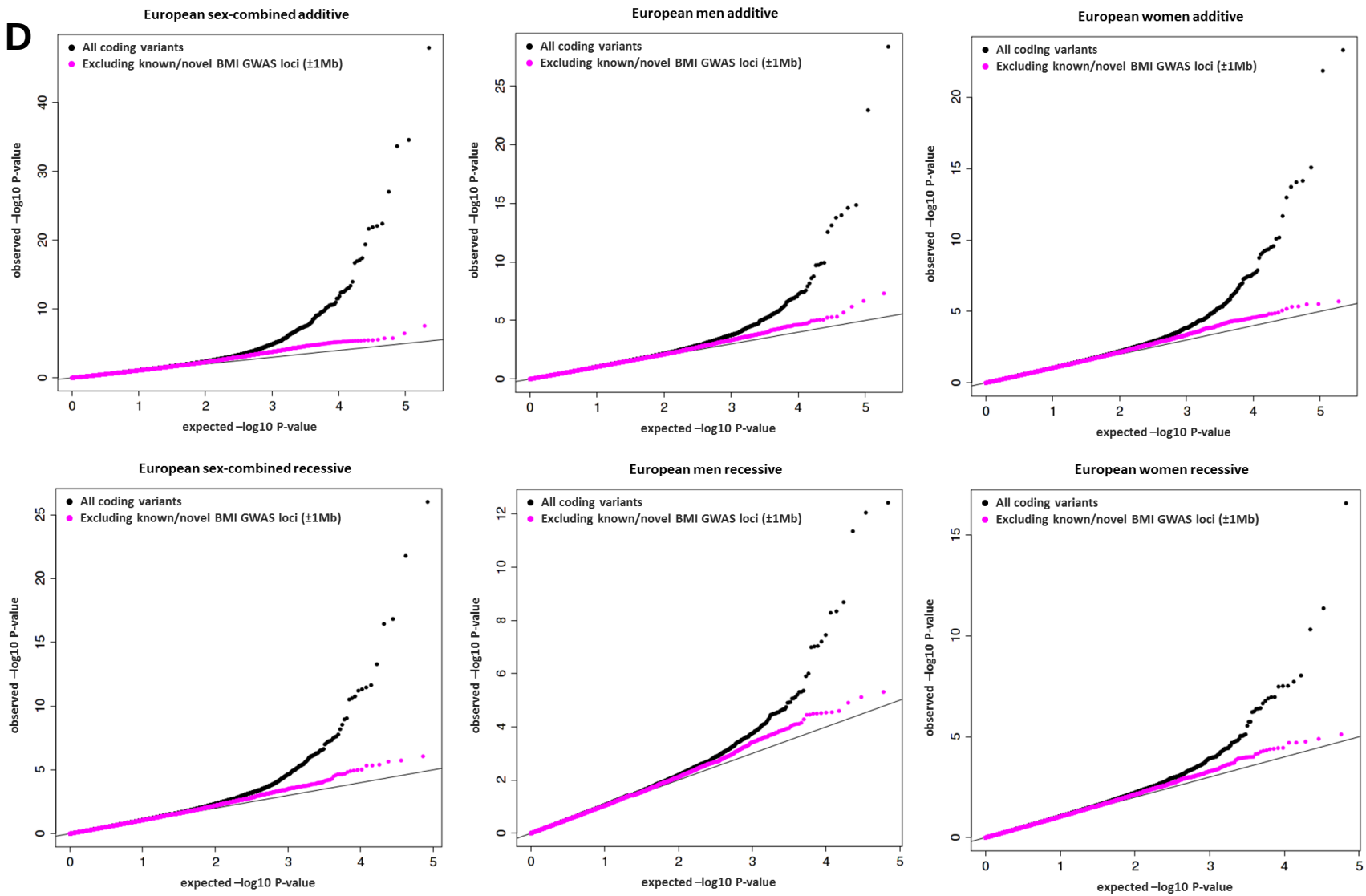
Supplementary Figure 2 | Quantile-quantile plots of BMI associations for coding SNVs tested in the Discovery GIANT meta-analyses. A-B. Quantile-quantile plots of BMI associations tested in all-ancestries (**A**) and European ancestry (**B**) strata for all coding (exonic and splicing) SNVs in black, and stratified by minor allele frequency (MAF) cut-offs; common variants (MAF≥5%) in green, rare and low-frequency variants (MAF<5%) in dark blue, and rare variants (MAF<1%) in light blue. **C-D.** Quantile-quantile plots of BMI associations tested in all-ancestries (C) and European ancestry (D) strata for all coding (exonic and splicing) SNVs in black, and after excluding (±1Mb) known and novel loci identified in previous BMI GWAS and in the ExomeChip meta-analysis (pink).


A
All ancestries sex-combined additive
All coding variants (N=229,703): λGC=1.10
Common (N=13,786): λGC=1.99
Low-frequency (N=9,612): λGC=1.41
Rare (N=206,305): λGC=1.05
All ancestries men additive
All coding variants (N=228,778): λGC=1.05
Common (N=13,747): λGC=1.53
Low-frequency (N=9,300): λGC=1.25
Rare (N=205,731): λGC=1.02
All ancestries women additive
All coding variants (N=228,796): λGC=1.07
Common (N=13,791): λGC=1.55
Low-frequency (N=9,916): λGC=1.28
Rare (N=205,089): λGC=1.04
All ancestries sex-combined recessive
All coding variants (N=119,552): λGC=1.05
Common (N=13,659): λGC=1.43
Low-frequency (N=7,423): λGC=1.07
Rare (N=98,470): λGC=1.00
All ancestries men recessive
All coding variants (N=98,588): λGC=1.04
Common (N=13,538): λGC=1.25
Low-frequency (N=6,574): λGC=1.03
Rare (N=78,476): λGC=1.01
All ancestries women recessive
All coding variants (N=99,710): λGC=1.03
Common (N=13,563): λGC=1.30
Low-frequency (N=7,208): λGC=1.02
Rare (N=78,939): λGC=1.00
observed –log10 P-value
expected –log10 P-value

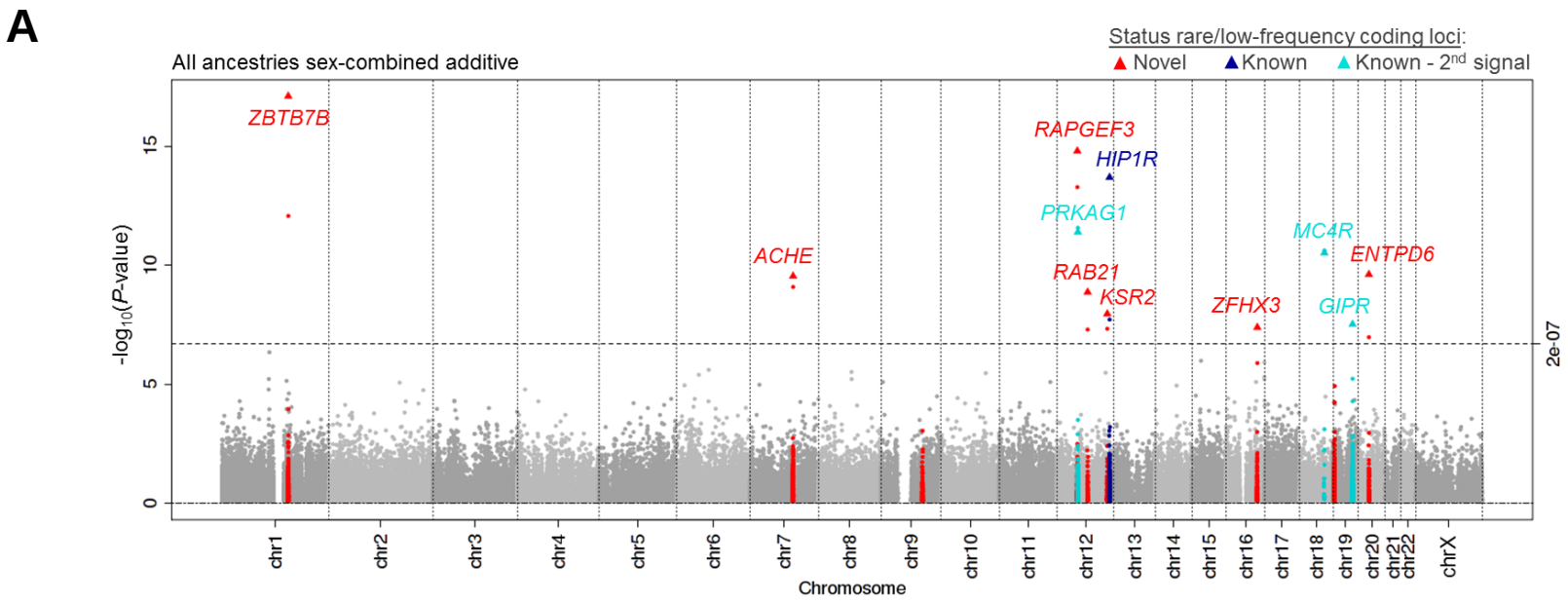
B


European sex-combined additive
All coding variants (N=225,218): λGC=1.09
Common (N=13,569): λGC=2.02
Low-frequency (N=8,940): λGC=1.45
Rare (N=202,709): λGC=1.04
European men additive
All coding variants (N=219,796): λGC=1.04
Common (N=13,584): λGC=1.59
Low-frequency (N=8,933): λGC=1.25
Rare (N=197,279): λGC=1.00
European women additive
All coding variants (N=220,383): λGC=1.06
Common (N=13,563): λGC=1.57
Low-frequency (N=8,921): λGC=1.27
Rare (N=197,899): λGC=1.03
European sex-combined recessive
All coding variants (N=83,965): λGC=1.05
Common (N=13,482): λGC=1.44
Low-frequency (N=6,667): λGC=1.03
Rare (N=63,816): λGC=0.99
European men recessive
All coding variants (N=69,235): λGC=1.05
Common (N=13,373): λGC=1.25
Low-frequency (N=5,940): λGC=1.04
Rare (N=49,922): λGC=1.00
European women recessive
All coding variants (N=66,708): λGC=1.03
Common (N=13,354): λGC=1.28
Low-frequency (N=6,084): λGC=0.98
Rare (N=47,270): λGC=0.98
observed –log10 P-value
expected –log10 P-value

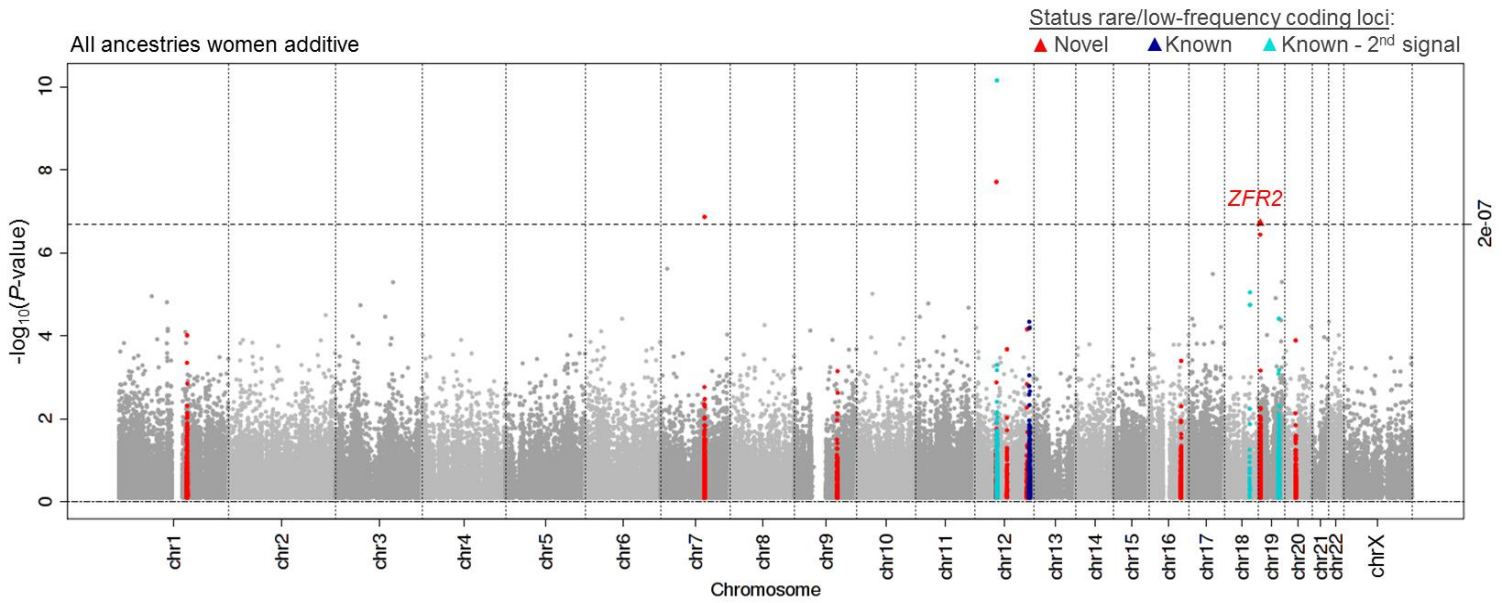

C
All ancestries sex-combined additive
All ancestries men additive
All ancestries women additive
All ancestries sex-combined recessive
All ancestries men recessive
All ancestries women recessive
All coding variants
Excluding known/novel BMI GWAS loci (±1Mb)
observed –log10 P-value
expected –log10 P-value


D
European sex-combined additive
European men additive
European women additive
European sex-combined recessive
European men recessive
European women recessive
All coding variants
Excluding known/novel BMI GWAS loci (±1Mb)
observed –log10 P-value
expected –log10 P-value

Supplementary Figure 3 | Manhattan plots of coding rare and low-frequency SNV associations in the Discovery GIANT dataset appended with the significant SNVs from the final combined meta-analysis. Manhattan plot of associations in all-ancestries sex-combined additive (A), all-ancestries women additive (B) and European ancestry sex-combined additive (C) strata. Each locus was defined using a 1Mb window on each side of the lead coding variant. Dots correspond to the Discovery GIANT meta-analysis results, while the final combined meta-analysis results were appended to the plots using triangles. Only significant loci in the final combined meta-analysis were colored; novel loci, secondary signals (in known GWAS loci, but independent from GWAS hit/proxy) and known loci were highlighted in red, light blue and dark blue, respectively.



B


All ancestries women additive
Status rare/low-frequency coding loci:
Novel
Known
Known - 2nd signal
ZFR2
2e-07
-log10(P-value)
Chromosome
chr1
chr2
chr3
chr4
chr5
chr6
chr7
chr8
chr9
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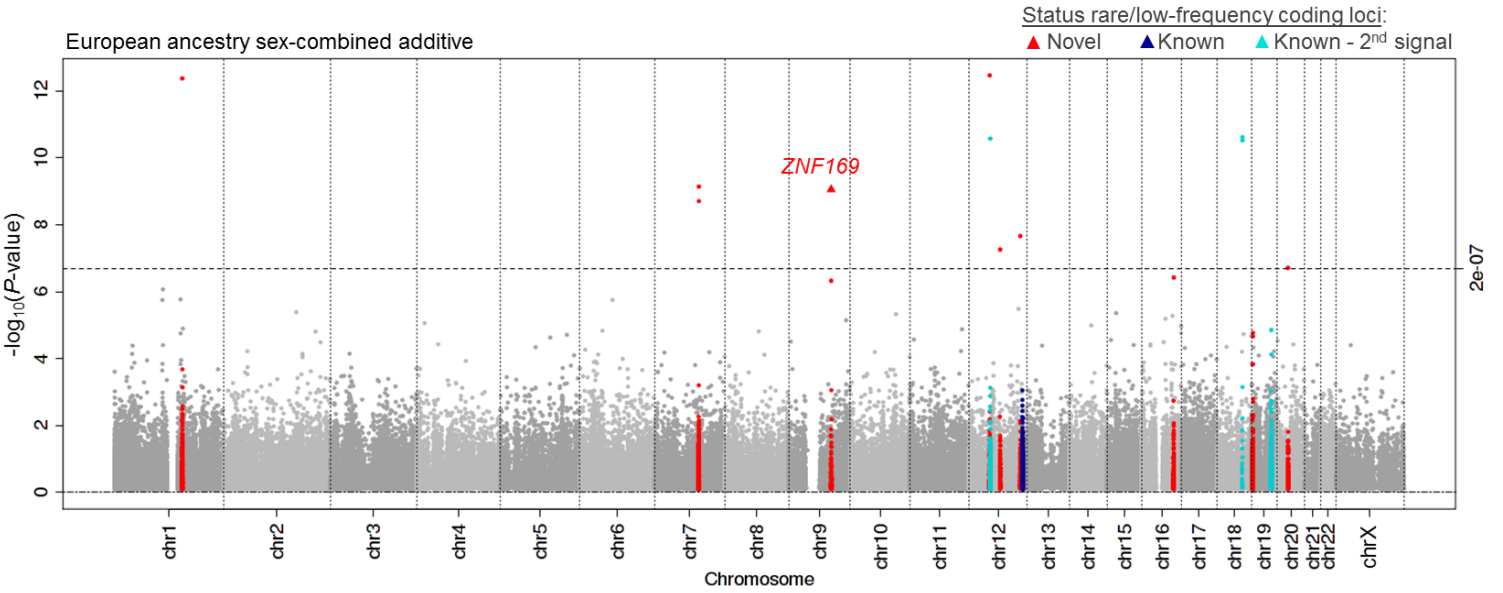
chr18
chr19
chr20
chr21
chr22
chrX

C

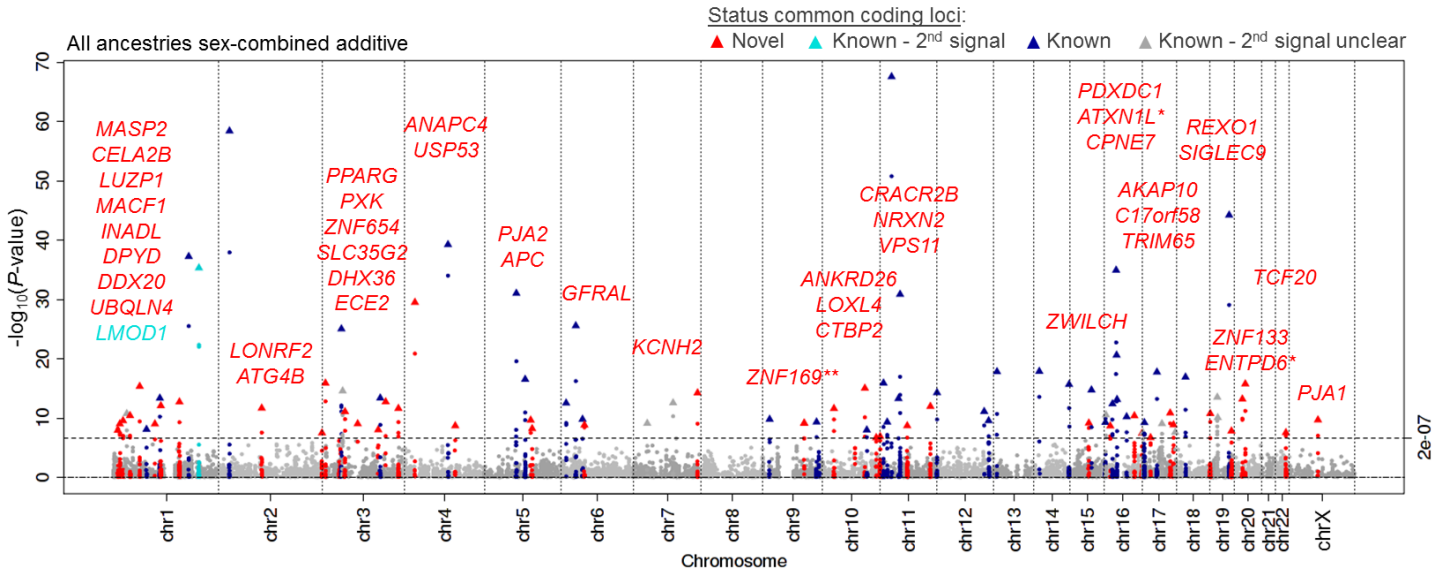

European ancestry sex-combined additive
Status rare/low-frequency coding loci:
Novel
Known
Known - 2nd signal
ZNF169
2e-07
-log10(P-value)
Chromosome
chr1
chr2
chr3
chr4
chr5
chr6
chr7
chr8
chr9
chr10
chr11
chr12
chr13
chr14
chr15
chr16
chr17
chr18
chr19
chr20
chr21
chr22
chrX

Supplementary Figure 4 | Manhattan plots of coding common SNV associations obtained in the Discovery GIANT dataset appended with the significant SNVs from the final combined meta-analysis See also Supplementary Table 4 for detailed results. Each locus was defined using a 1Mb window on each side of the lead coding variant. Dots correspond to the Discovery GIANT meta-analysis results, while the final combined meta-analysis results were appended to the plots using triangles.

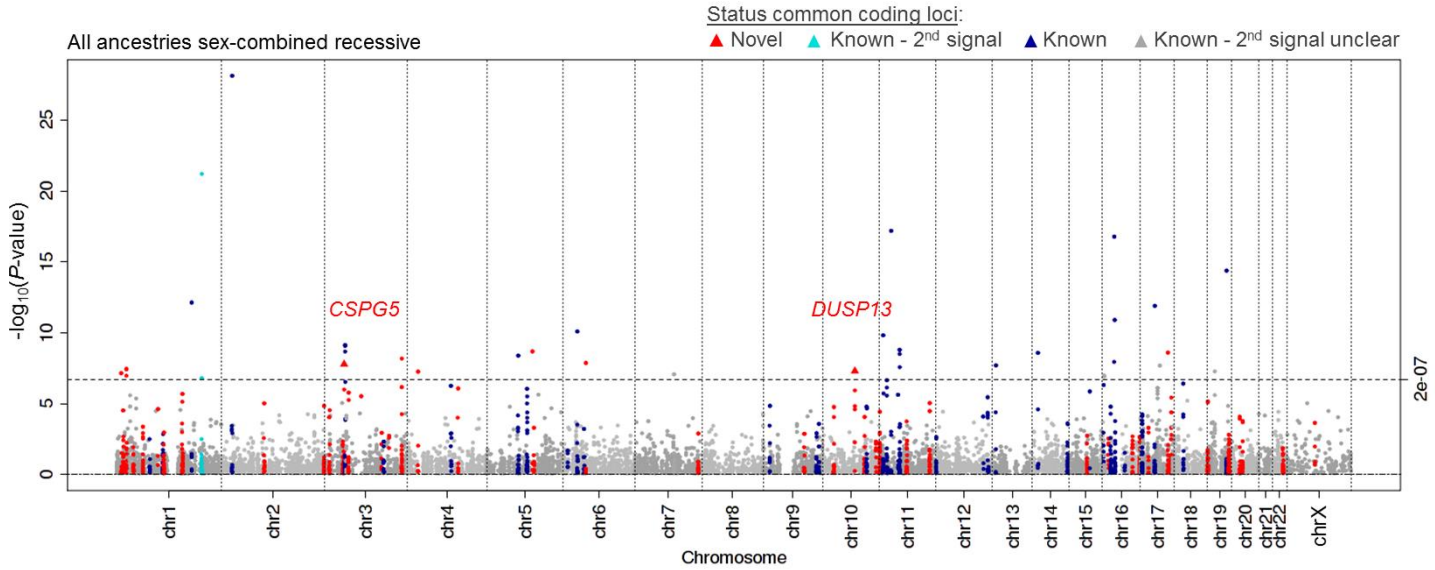
Panels A, B & C: Results from novel loci and novel secondary signals. Manhattan plot of associations in all-ancestries sex-combined additive (A), all-ancestries sex-combined recessive (B) and European ancestry sex-combined additive (C) strata. Only novel loci (in red) and novel secondary signals in known loci (in cyan) are shown in panels A, B & C.

Panels D & E: Results from known loci, some of which with potential secondary signals. Manhattan plot of associations in all-ancestries sex-combined additive (D) and all-ancestries women additive (E) strata. Loci that were previously established (in blue), and signals in previously known loci, but for which conditional analyses could not convincingly determine whether the signal was secondary or the same locus (in grey) are shown in panels D & E.

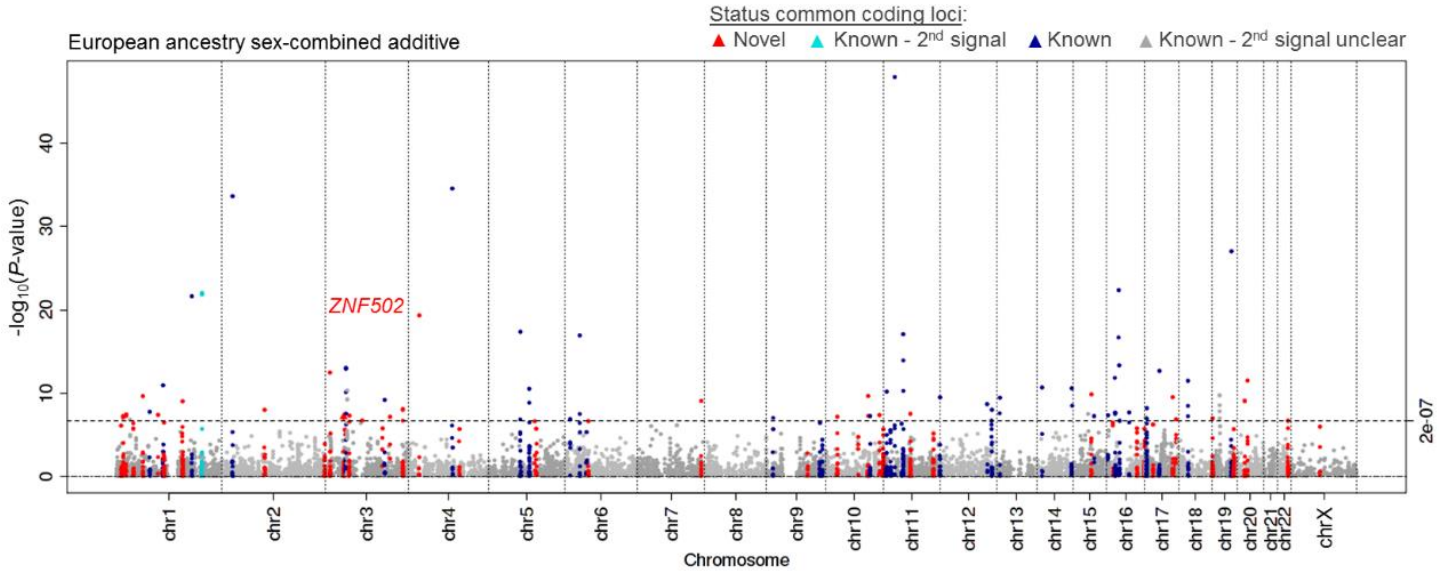
A


All ancestries sex-combined additive
Status common coding loci:
Novel
Known - 2nd signal
Known
Known - 2nd signal unclear
-log10(P-value)
Chromosome
2e-07
MASP2
CELA2B
LUZP1
MACF1
INADL
DPYD
DDX20
UBQLN4
LMOD1
LONRF2
ATG4B
PPARG
PXK
ZNF654
SLC35G2
DHX36
ECE2
ANAPC4
USP53
PJA2
APC
GFRAL
KCNH2
ZNF169**
ANKRD26
LOXL4
CTBP2
CRACR2B
NRXN2
VPS11
PDXDC1
ATXN1L*
CPNE7
REXO1
SIGLEC9
AKAP10
C17orf58
TRIM65
ZWILCH
TCF20
ZNF133
ENTPD6*
PJA1

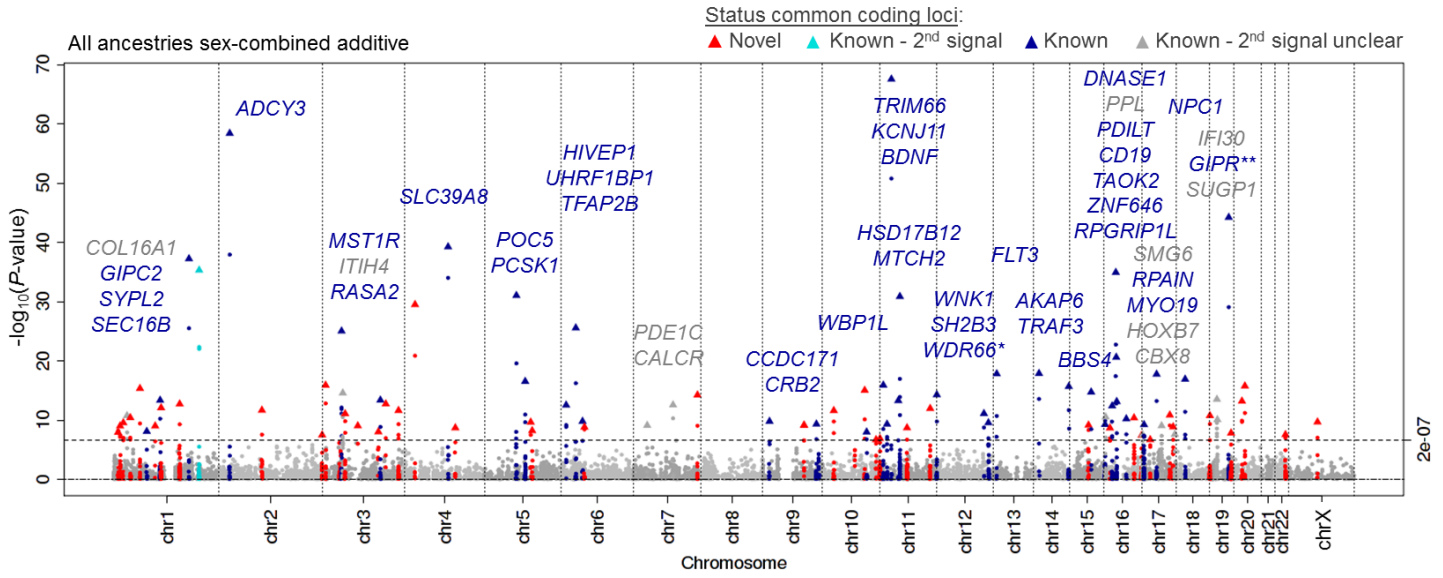
B


All ancestries sex-combined recessive
Status common coding loci:
Novel
Known - 2nd signal
Known
Known - 2nd signal unclear
-log10(P-value)
Chromosome
2e-07
CSPG5
DUSP13

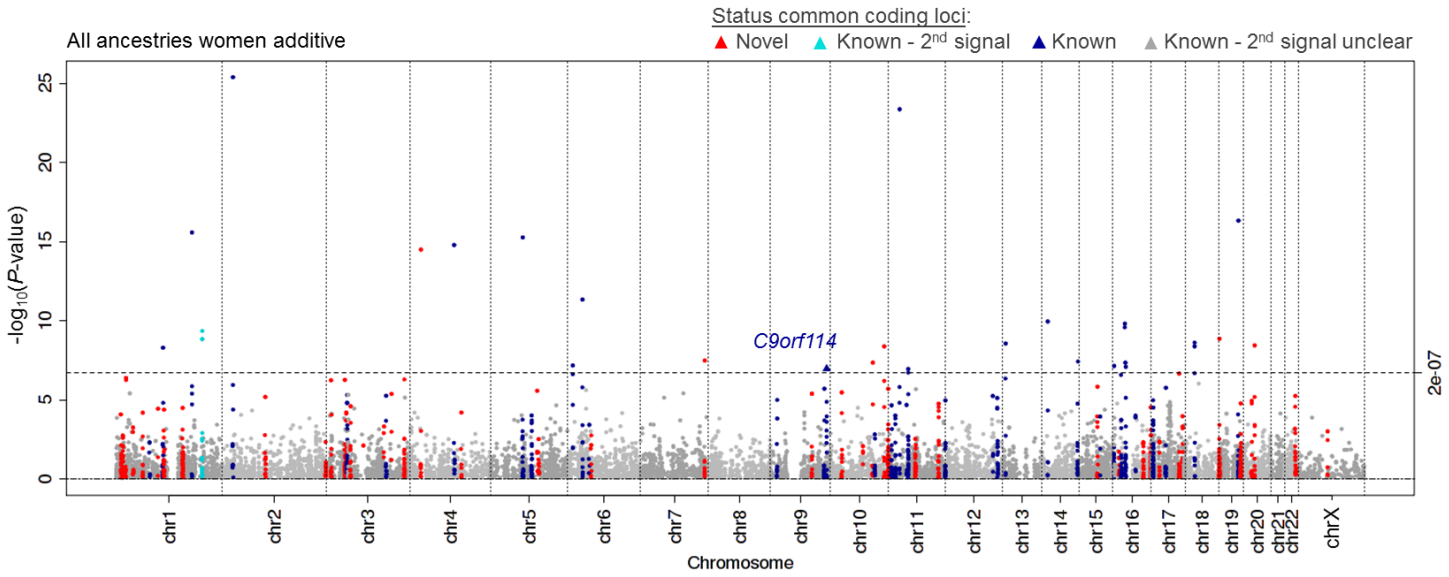
C


European ancestry sex-combined additive
Status common coding loci:
Novel
Known - 2nd signal
Known
Known - 2nd signal unclear
-log10(P-value)
ZNF502
2e-07
chr1
chr2
chr3
chr4
chr5
chr6
chr7
chr8
chr9
chr10
chr11
chr12
chr13
chr14
chr15
chr16
chr17
chr18
chr19
chr20
chr21
chr22
chrX
Chromosome

D

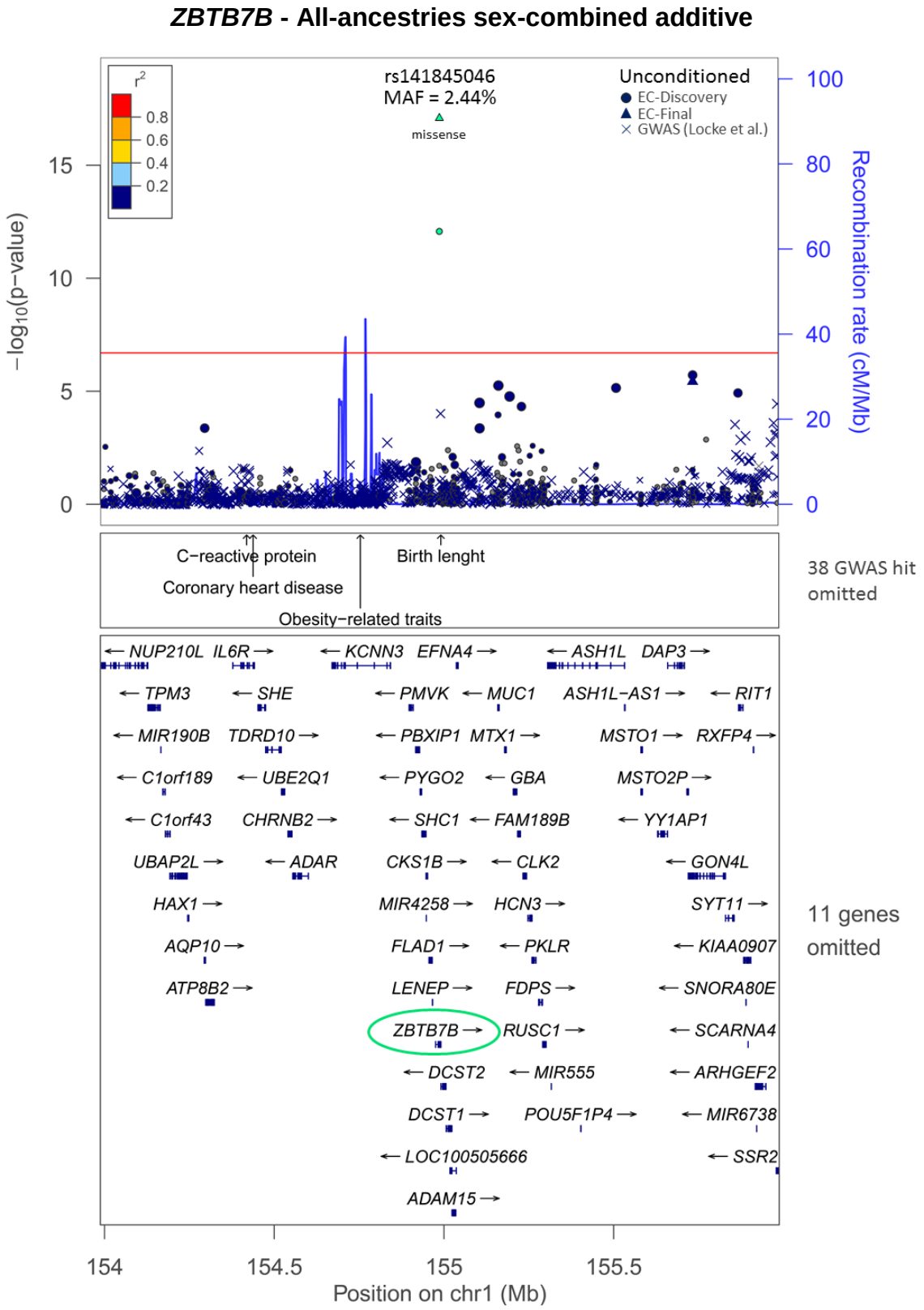

All ancestries sex-combined additive
Status common coding loci:
Novel
Known - 2nd signal
Known
Known - 2nd signal unclear
-log10(P-value)
ADCY3
COL16A1
GIPC2
SYPL2
SEC16B
MST1R
ITIH4
RASA2
SLC39A8
POC5
PCSK1
HIVEP1
UHRF1BP1
TFAP2B
PDE1C
CALCR
CCDC171
CRB2
WBP1L
TRIM66
KCNJ11
BDNF
HSD17B12
MTCH2
WNK1
SH2B3
WDR66*
FLT3
AKAP6
TRAF3
BBS4
DNASE1
PPL
NPC1
PDILT
CD19
TAOK2
ZNF646
RPGRIP1L
IFI30
GIPR**
SUGP1
SMG6
RPAIN
MYO19
HOXB7
CBX8
2e-07
chr1
chr2
chr3
chr4
chr5
chr6
chr7
chr8
chr9
chr10
chr11
chr12
chr13
chr14
chr15
chr16
chr17
chr18
chr19
chr20
chr21
chr22
chrX
Chromosome

E

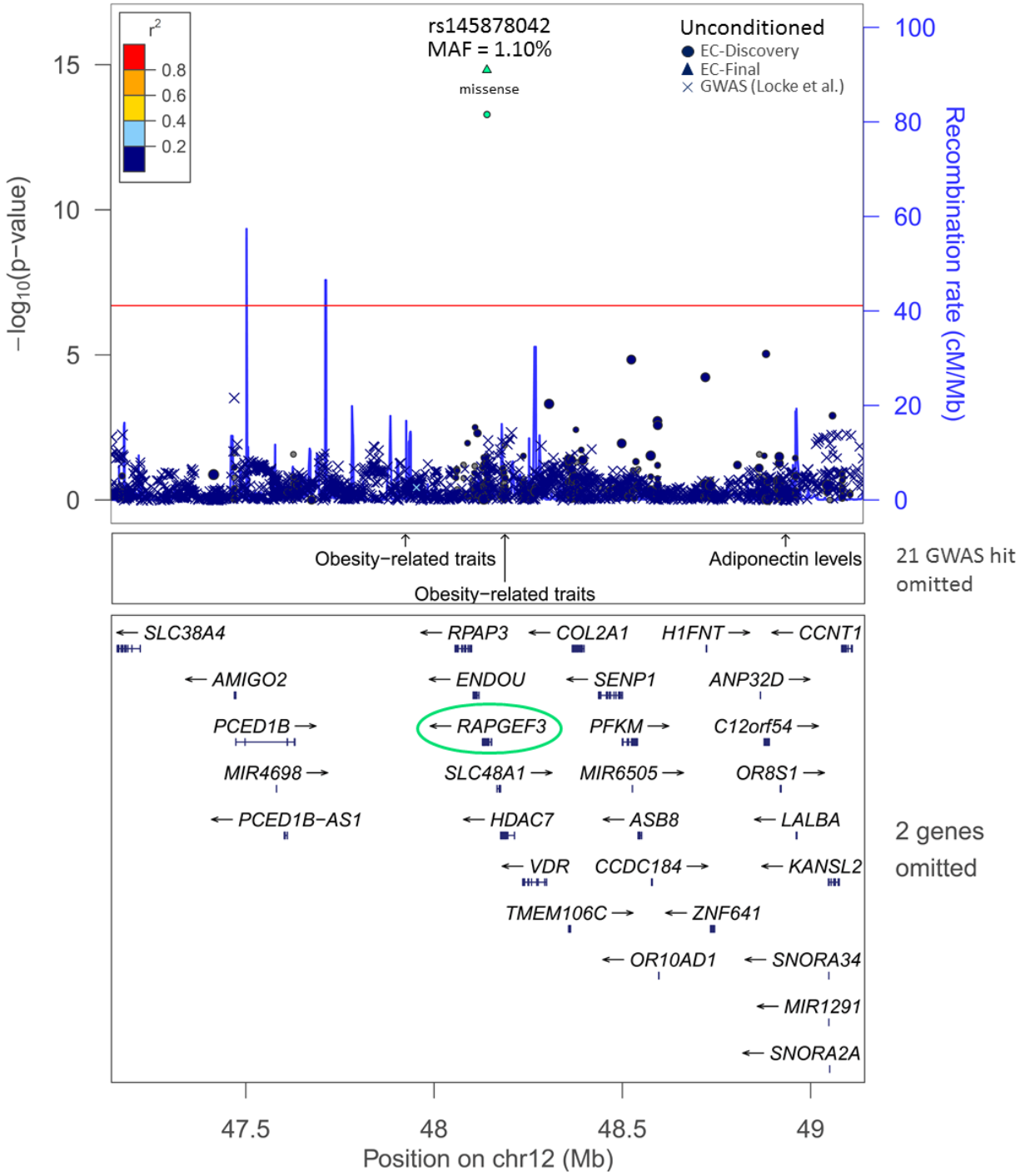

All ancestries women additive
Status common coding loci:
Novel
Known - 2nd signal
Known
Known - 2nd signal unclear
-log10(P-value)
0
5
10
15
20
25
C9orf114
2e-07
chr1
chr2
chr3
chr4
chr5
chr6
chr7
chr8
chr9
chr10
chr11
chr12
chr13
chr14
chr15
chr16
chr17
chr18
chr19
chr20
chr21
chr22
chrX
Chromosome

Supplementary Figure 5 | Regional association plots for the significant rare and low-frequency coding loci identified in the final combined meta-analysis among all analysis strata. The association results shown in these plots are from the Discovery GIANT meta-analysis in the specified analysis strata for all ExomeChip SNVs (dots) and appended with the previous BMI GWAS results (European ancestry) from Locke et al. (crosses; Locke et al. Nature 518, 197-206). The size of the dots and crosses are weighted on the minor allele frequency. We have used the UK Biobank dataset (European ancestry; N=136,727) to calculate the linkage disequilibrium between the SNVs in the window and the reference coding SNV shown in turquoise. Only GWAS traits related with body weight are shown in the plots. (A) Regional plots for loci with only one significant coding SNV in the region (only unconditioned results shown). (B) Regional plots for loci with more than one significant coding SNVs or with a GWAS hit or proxy (r^2>0.80 in EUR 1000G phase 3) in the region (<±1MB). Both unconditioned and conditioned results are shown.

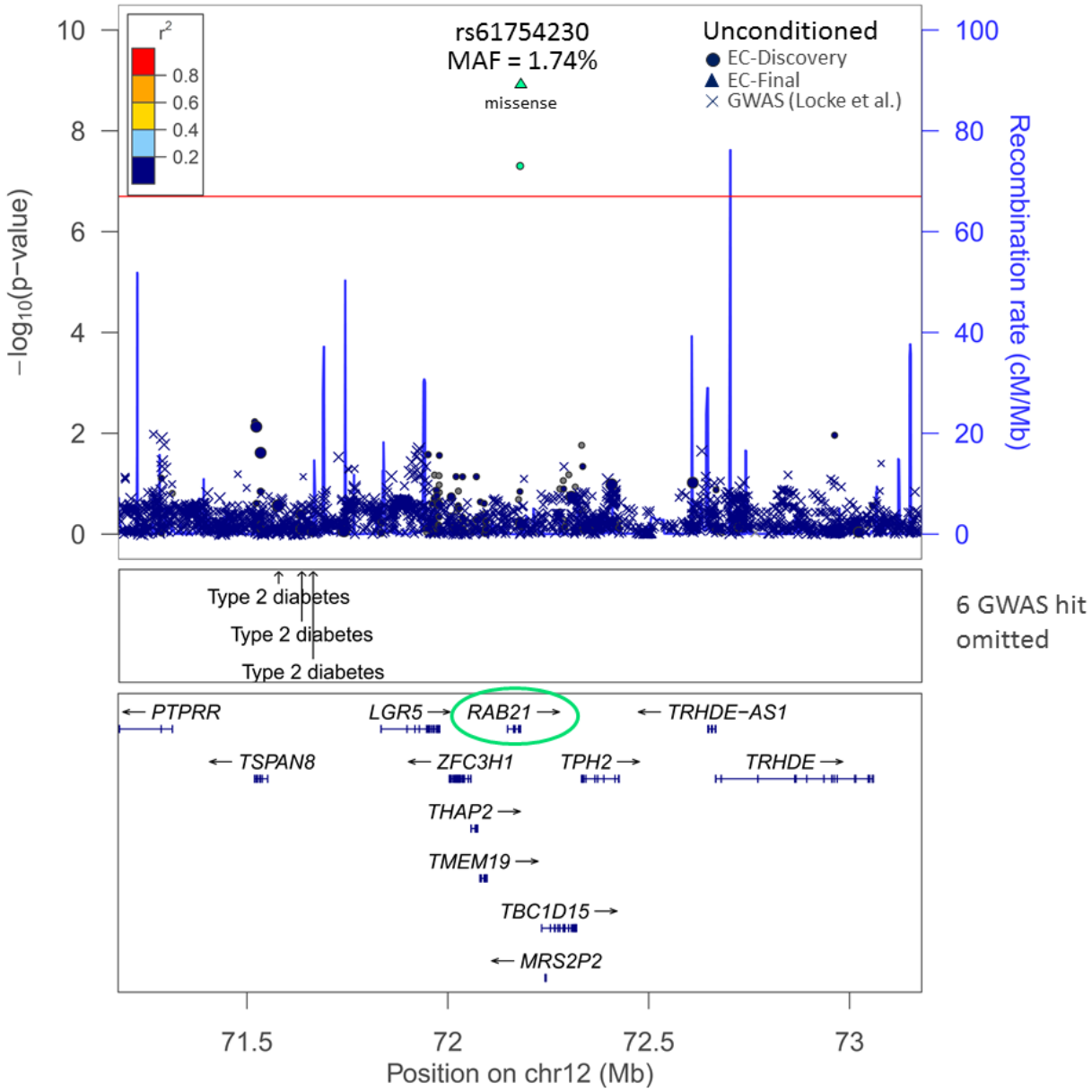
A


ZBTB7B - All-ancestries sex-combined additive
rs141845046
MAF = 2.44%
missense
Unconditioned
EC-Discovery
EC-Final
GWAS (Locke et al.)
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
C−reactive protein
Coronary heart disease
Birth lenght
Obesity−related traits
38 GWAS hit omitted
NUP210L IL6R KCNN3 EFNA4 ASH1L DAP3
TPM3 SHE PMVK MUC1 ASH1L-AS1 RIT1
MIR190B TDRD10 PBXIP1 MTX1 MSTO1 RXFP4
C1orf189 UBE2Q1 PYGO2 GBA MSTO2P
C1orf43 CHRNB2 SHC1 FAM189B YY1AP1
UBAP2L ADAR CKS1B CLK2 GON4L
HAX1 MIR4258 HCN3 SYT11
AQP10 FLAD1 PKLR KIAA0907
ATP8B2 LENEP FDPS SNORA80E
ZBTB7B RUSC1 SCARNA4
DCST2 MIR555 ARHGEF2
DCST1 POU5F1P4 MIR6738
LOC100505666 SSR2
ADAM15
11 genes omitted
154
154.5
155
155.5
Position on chr1 (Mb)

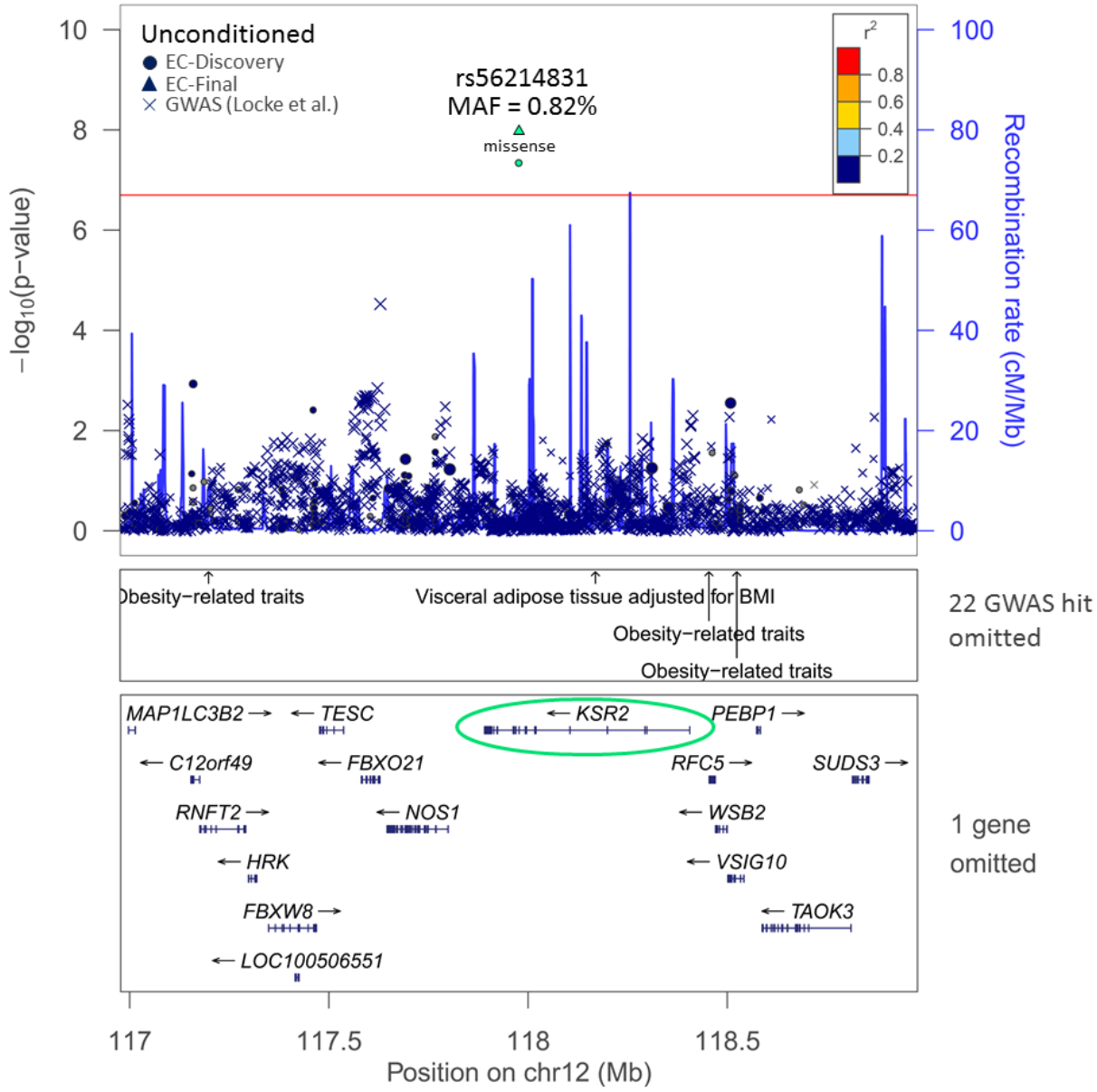
RAPGEF3 - All-ancestries sex-combined additive



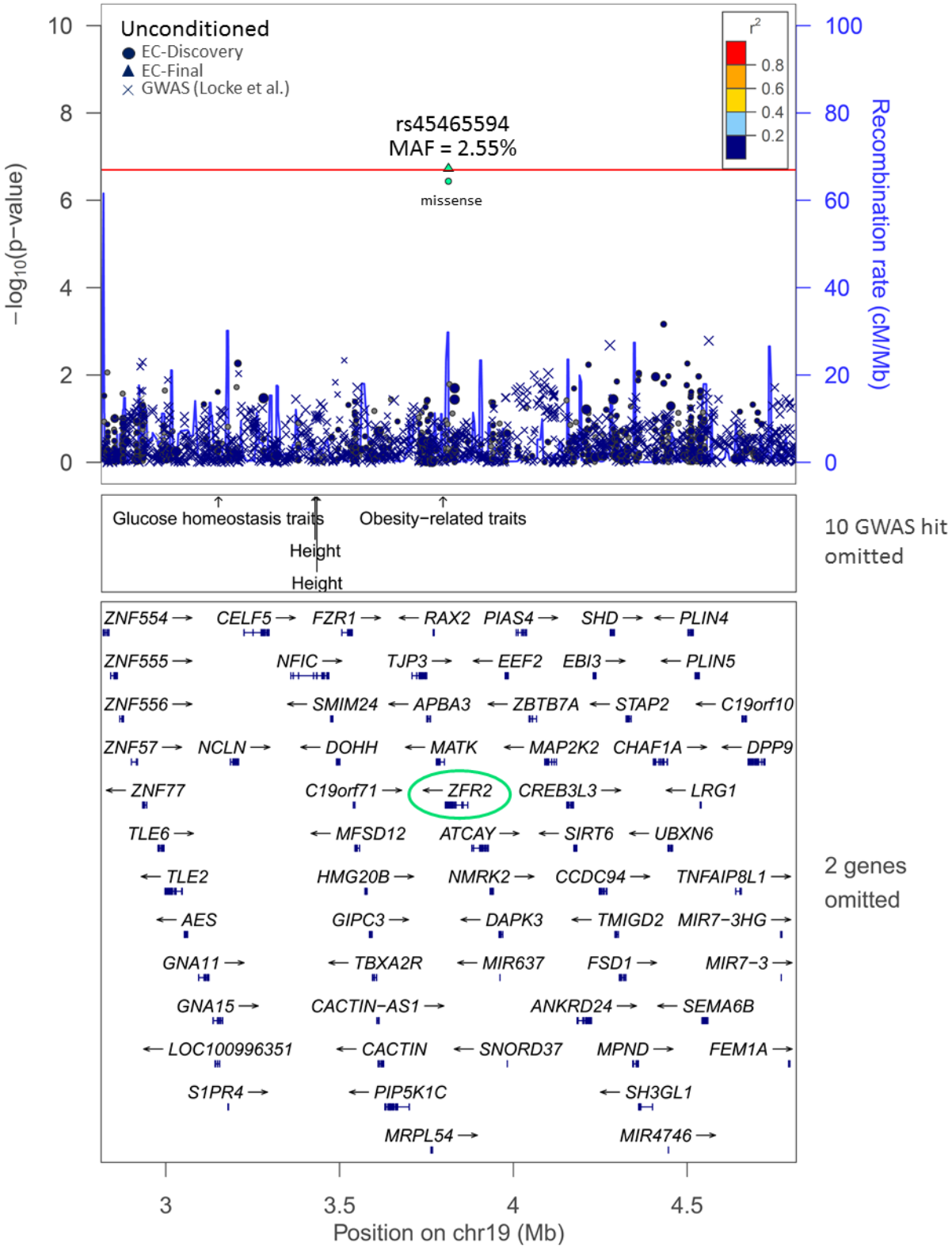
RAB21 - All-ancestries sex-combined additive



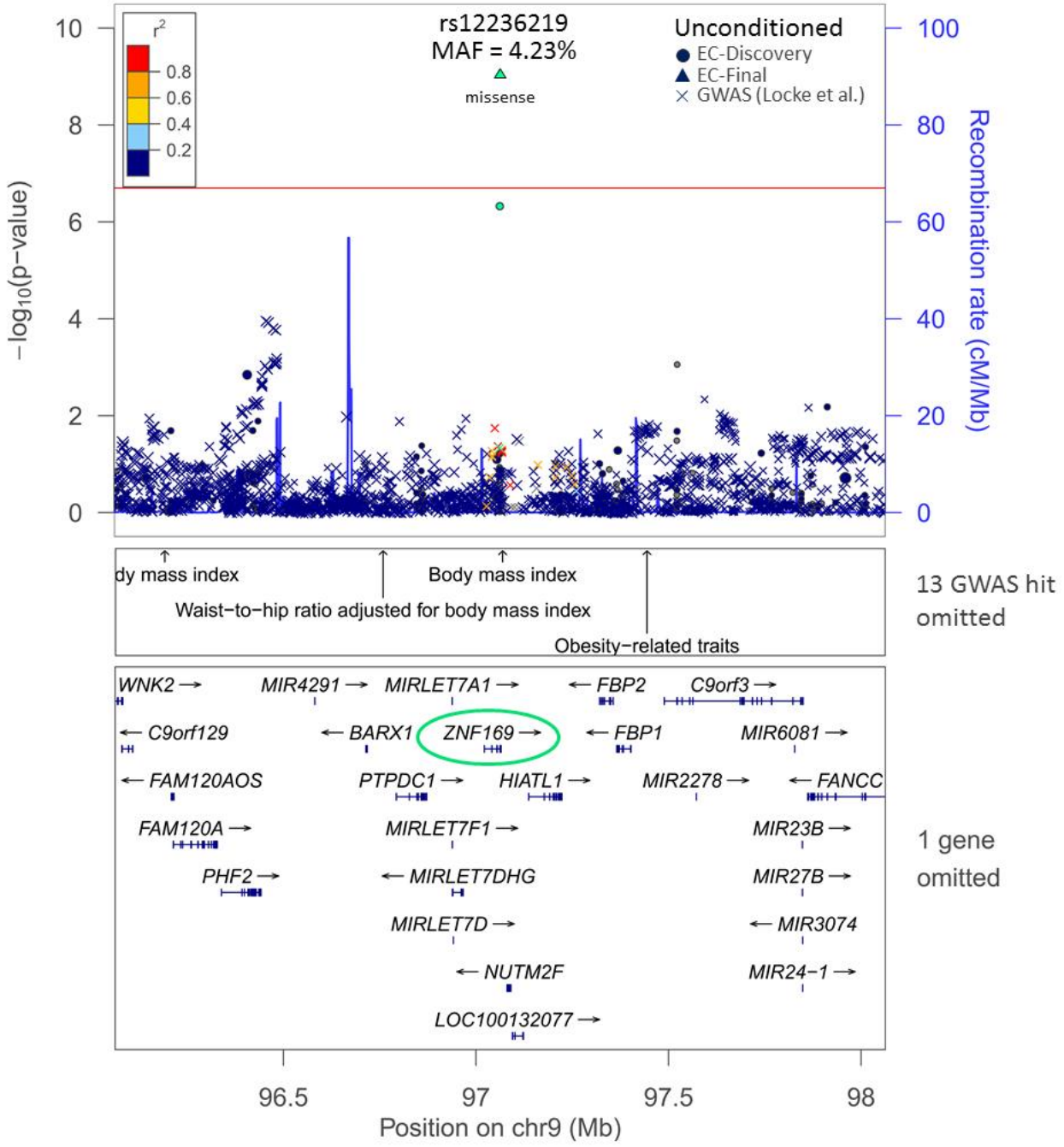
KSR2 - All-ancestries sex-combined additive



ZFR2 - All-ancestries women additive

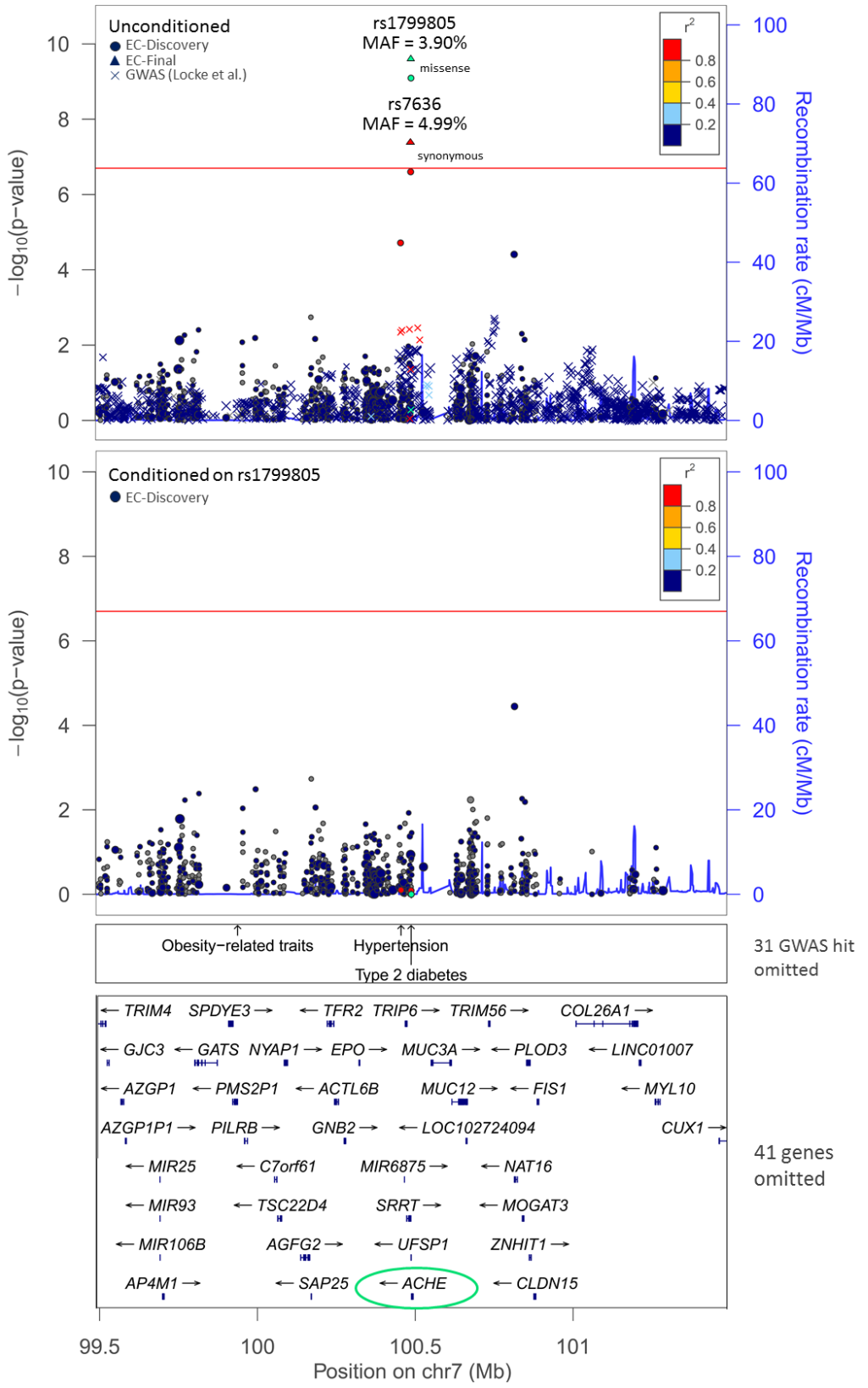


ZNF169 - Europeans sex-combined additive

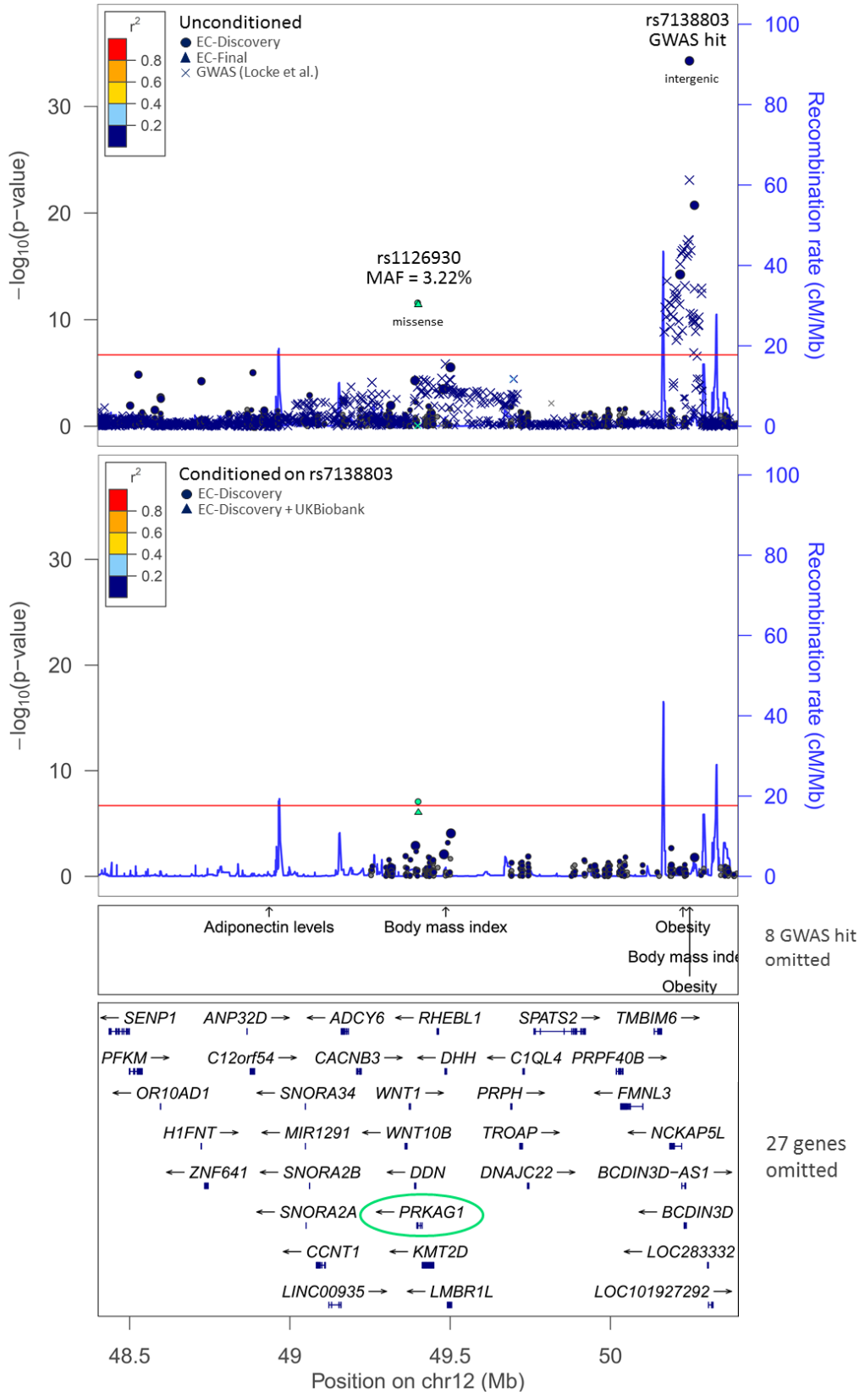


B

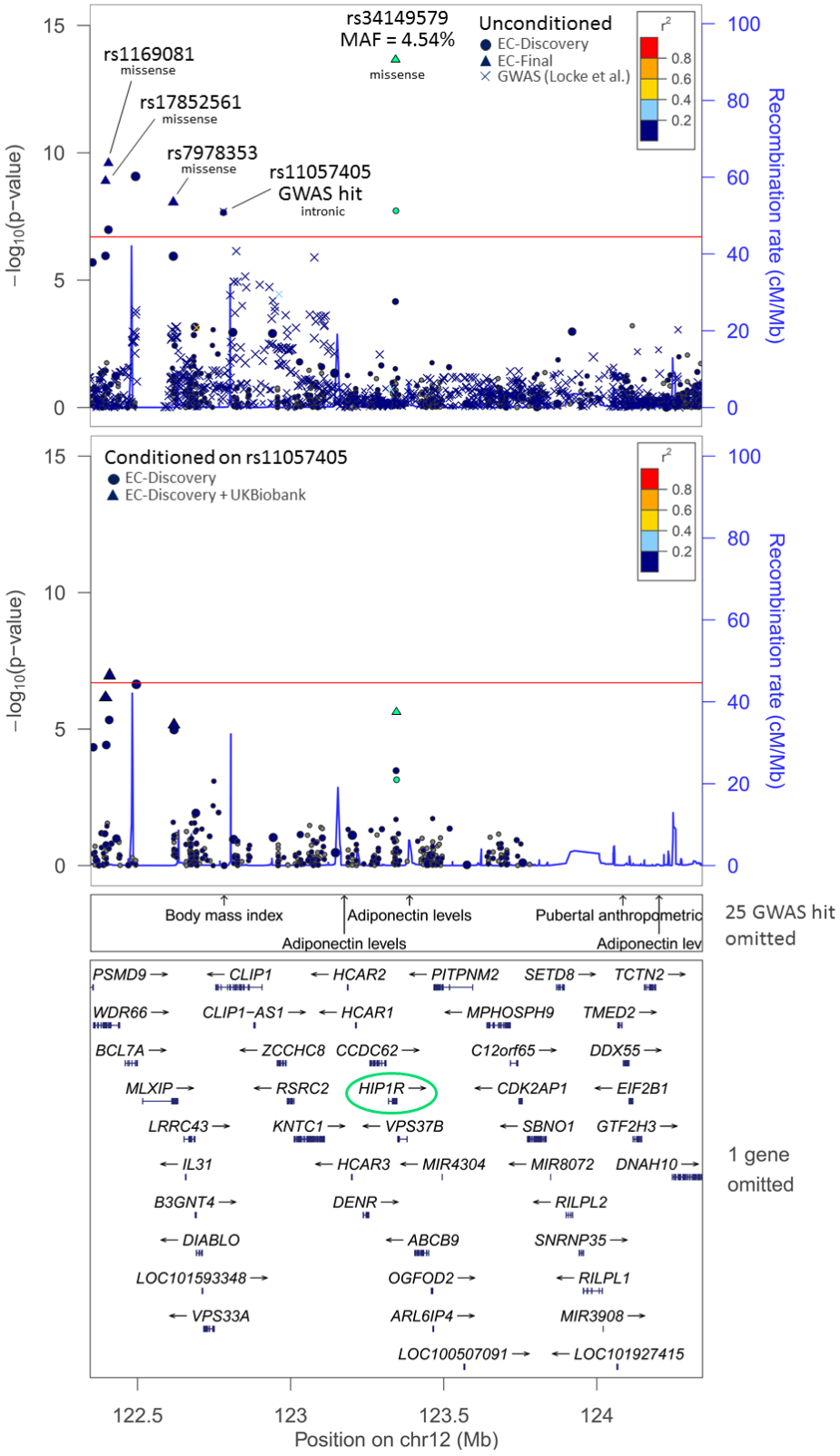
ACHE - All-ancestries sex-combined additive



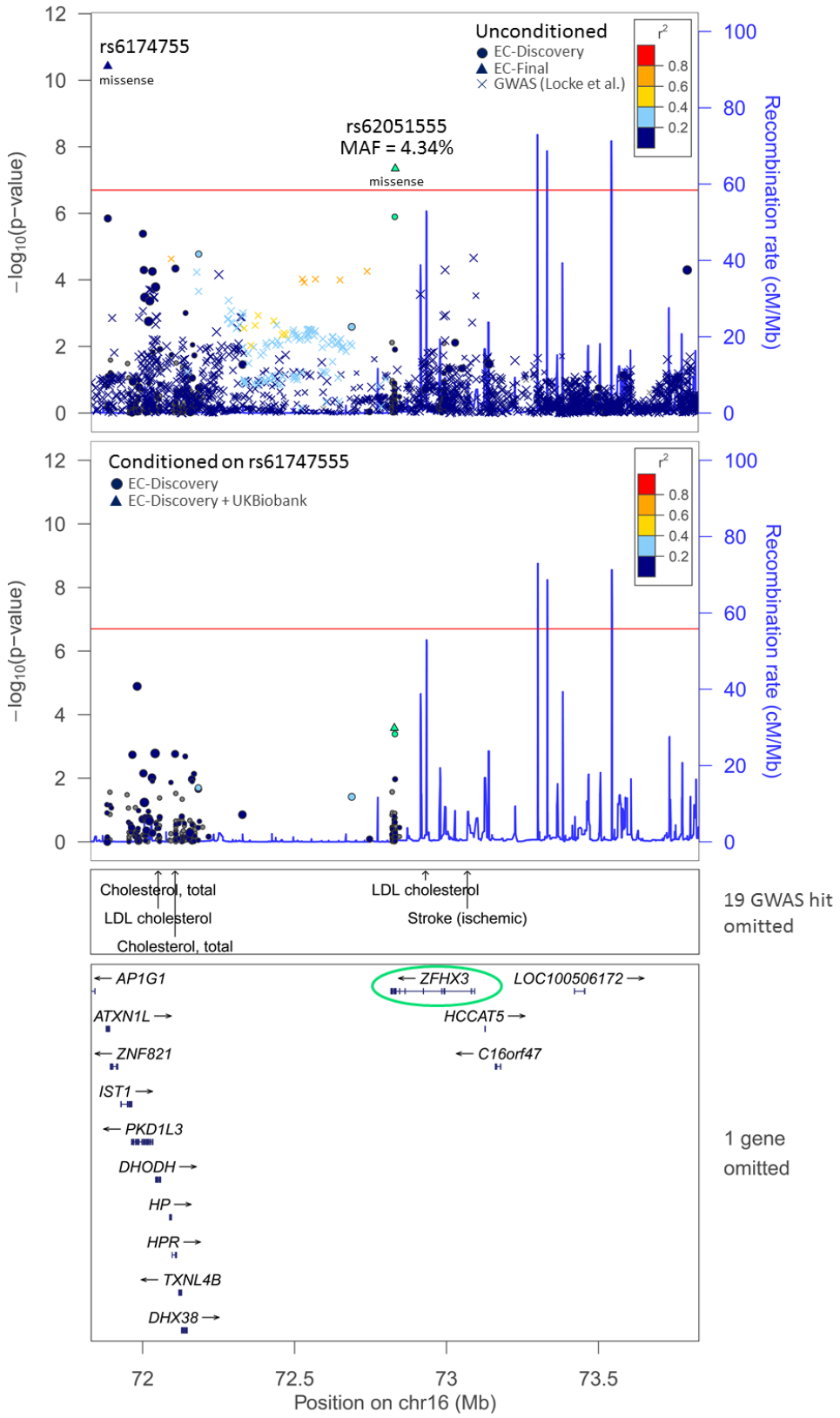
PRKAG1 - All-ancestries sex-combined additive



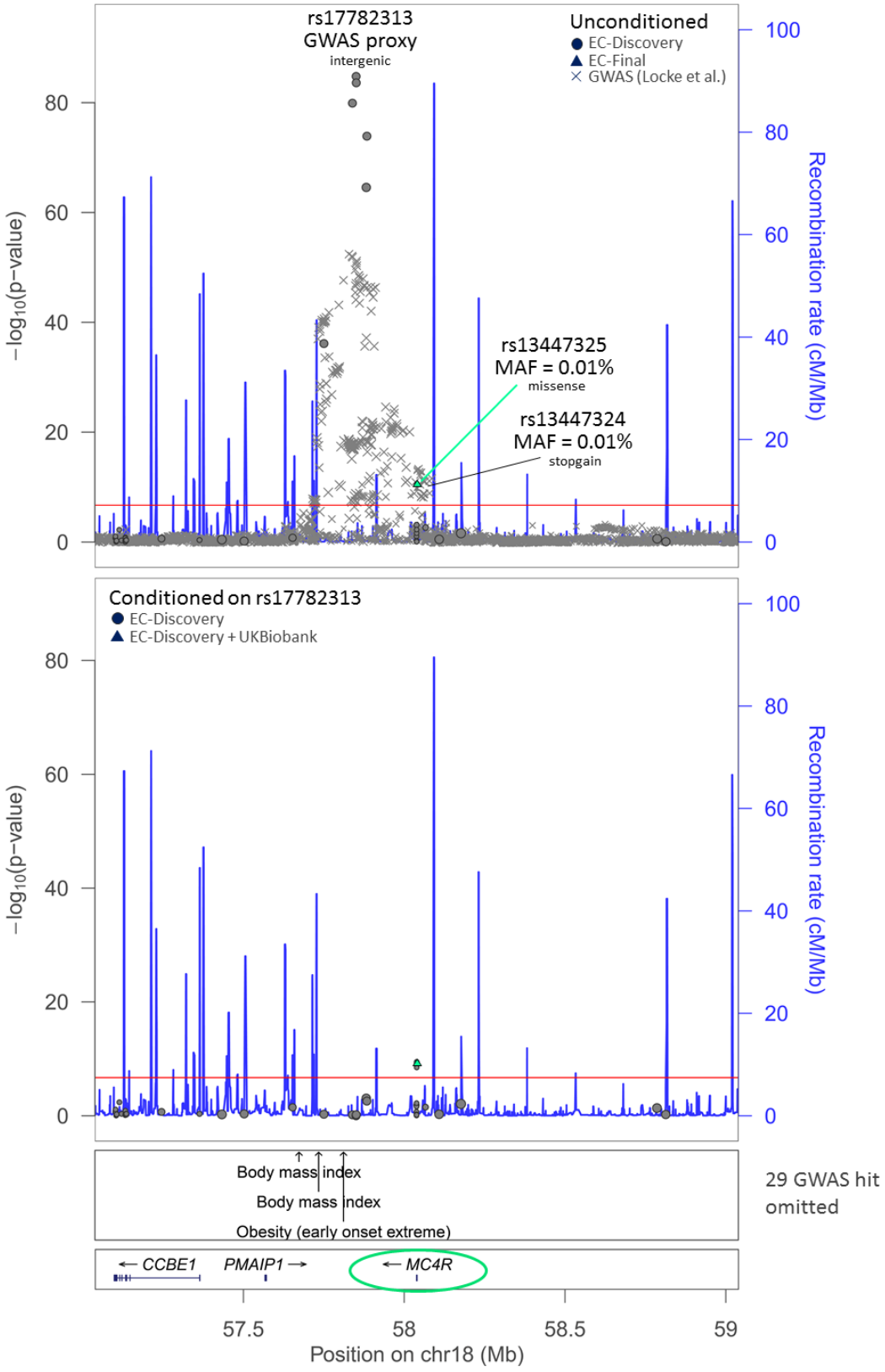
HIP1R - All-ancestries sex-combined additive



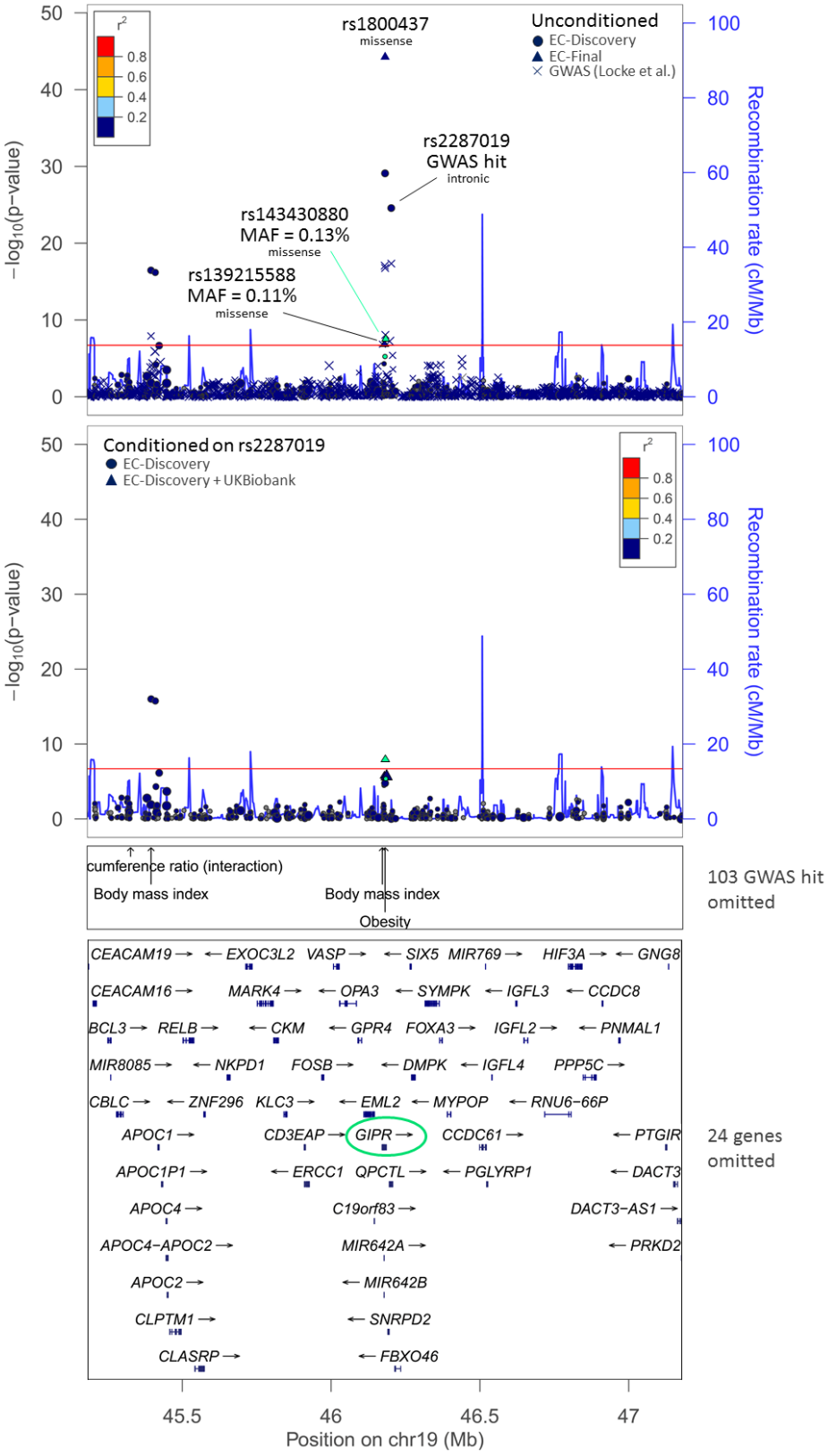
ZFHX3 - All-ancestries sex-combined additive



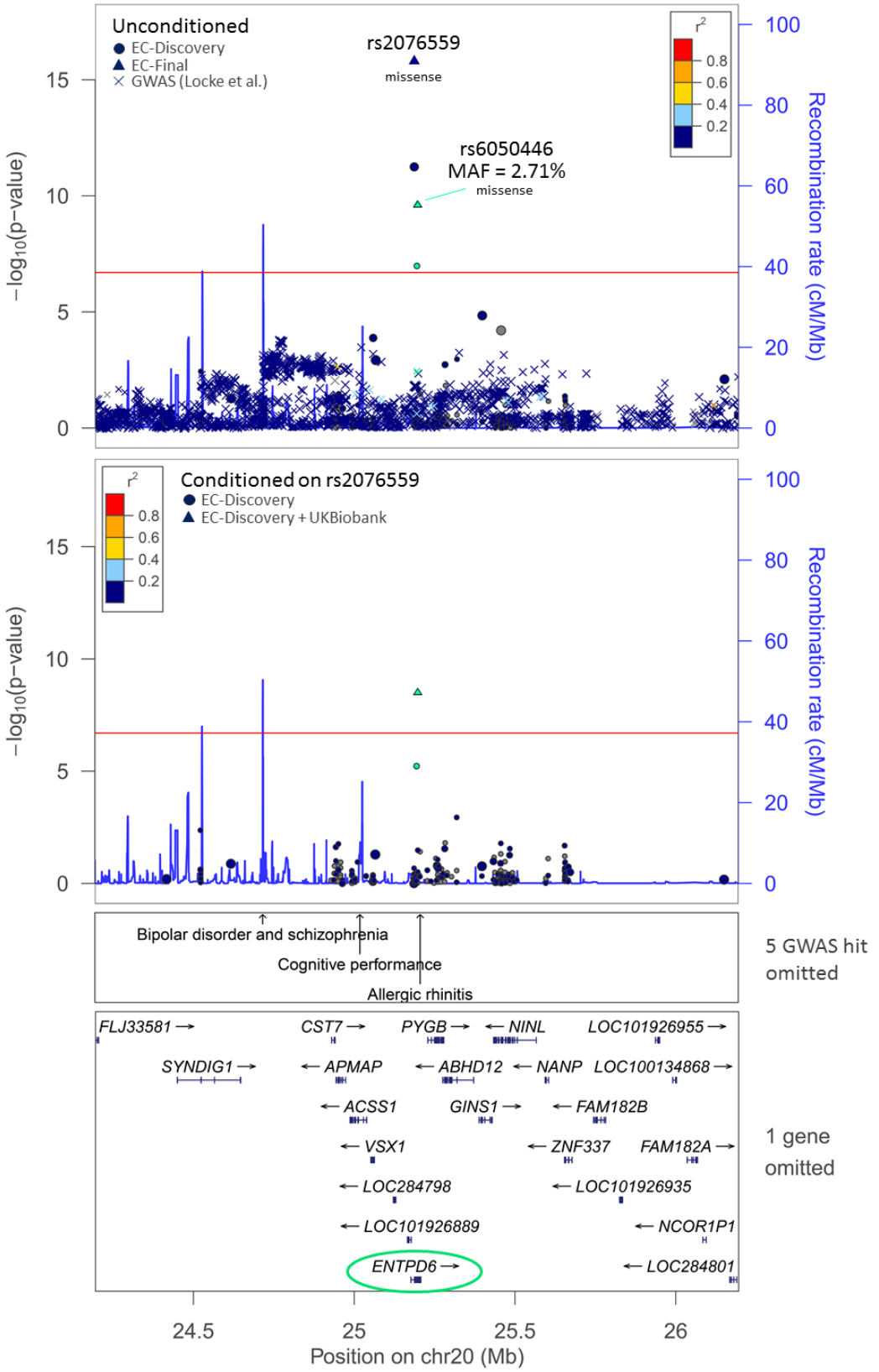
MC4R - All-ancestries sex-combined additive



GIPR - All-ancestries sex-combined additive

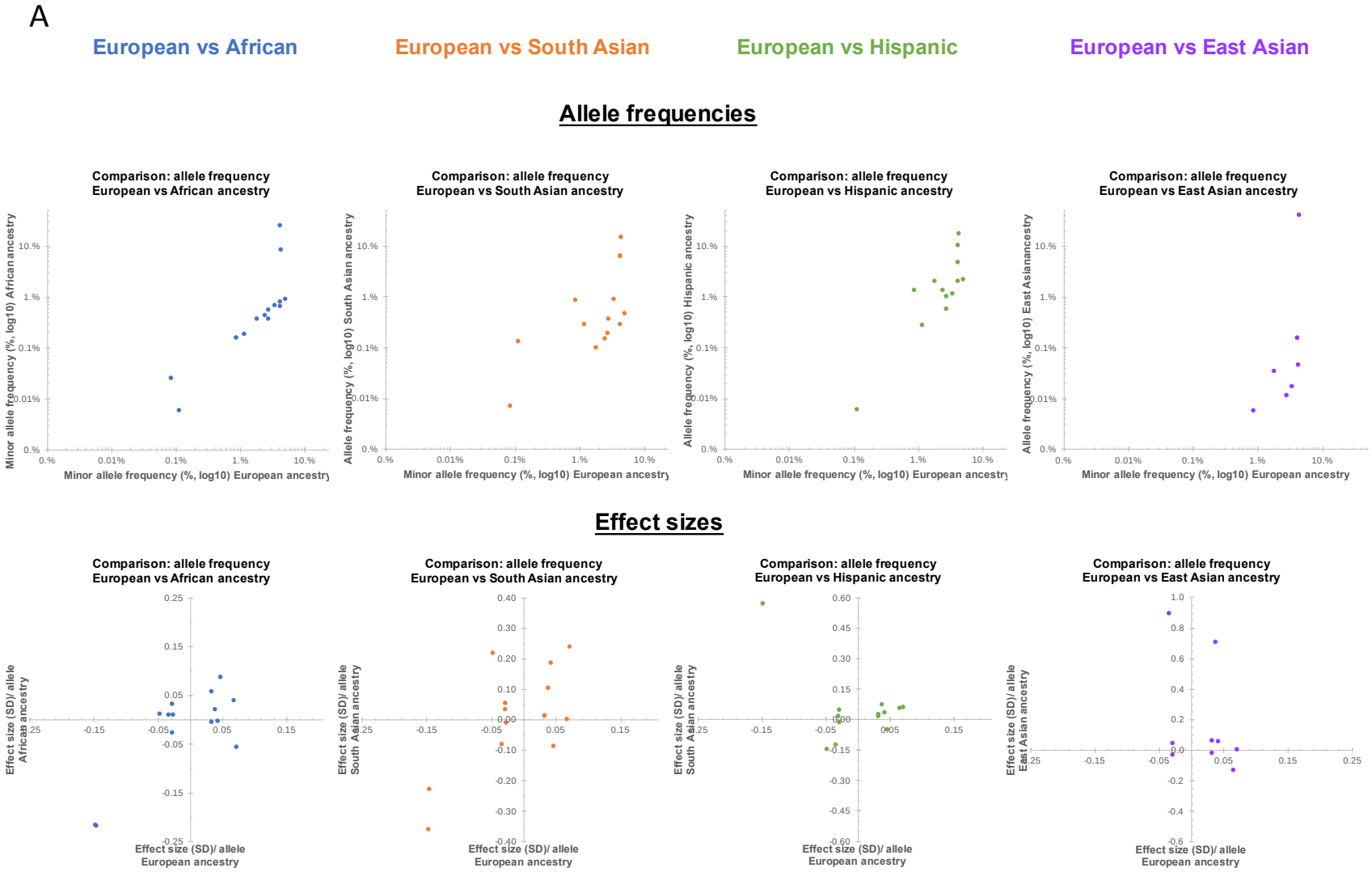


ENTPD6 - All-ancestries sex-combined additive



Supplementary Figure 6 | Relationship of allele frequencies and effect sizes of novel SNVs between European-ancestry and other ancestry populations (see also Supplementary Table 7). Panel A shows the data for the minor alleles of 14 low-frequency and rare SNVs. Panel B shows the data for the BMI-increasing allele of the 41 common SNVs.

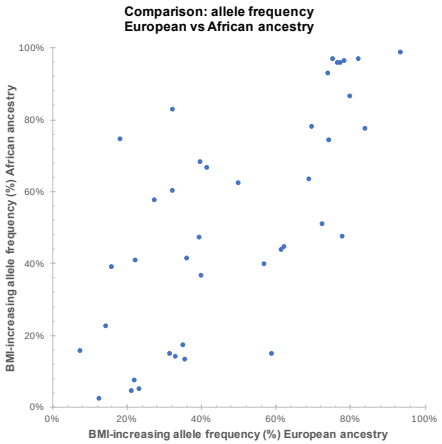
A

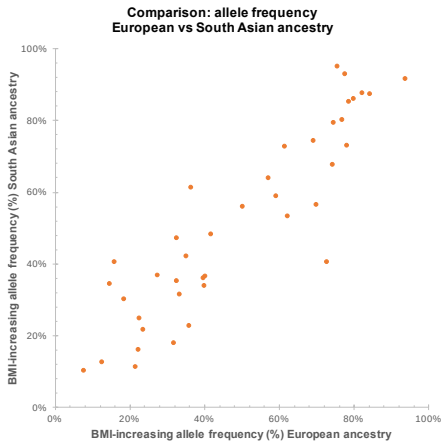


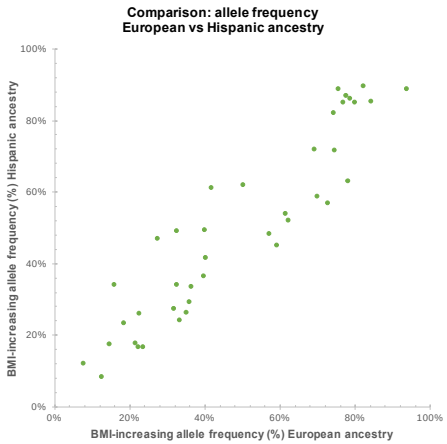
B

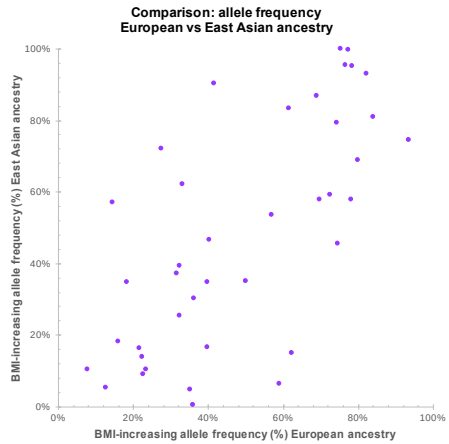
European vs African | European vs South Asian | European vs Hispanic | European vs East Asian

Allele frequencies

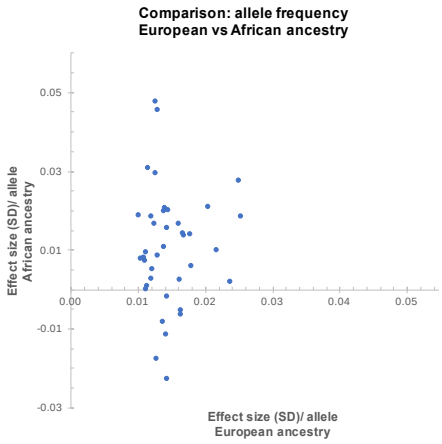


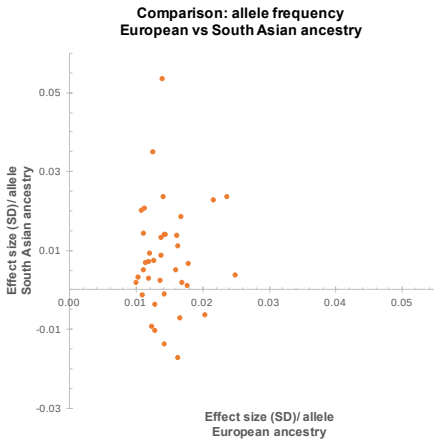


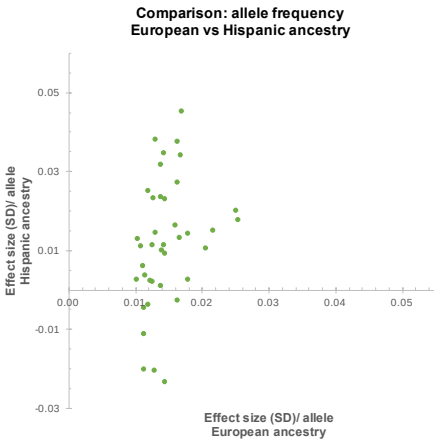


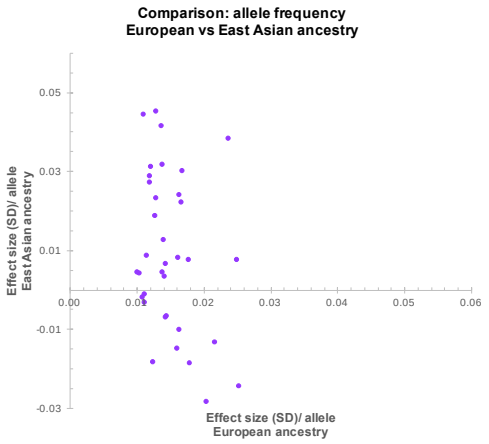


Effect sizes

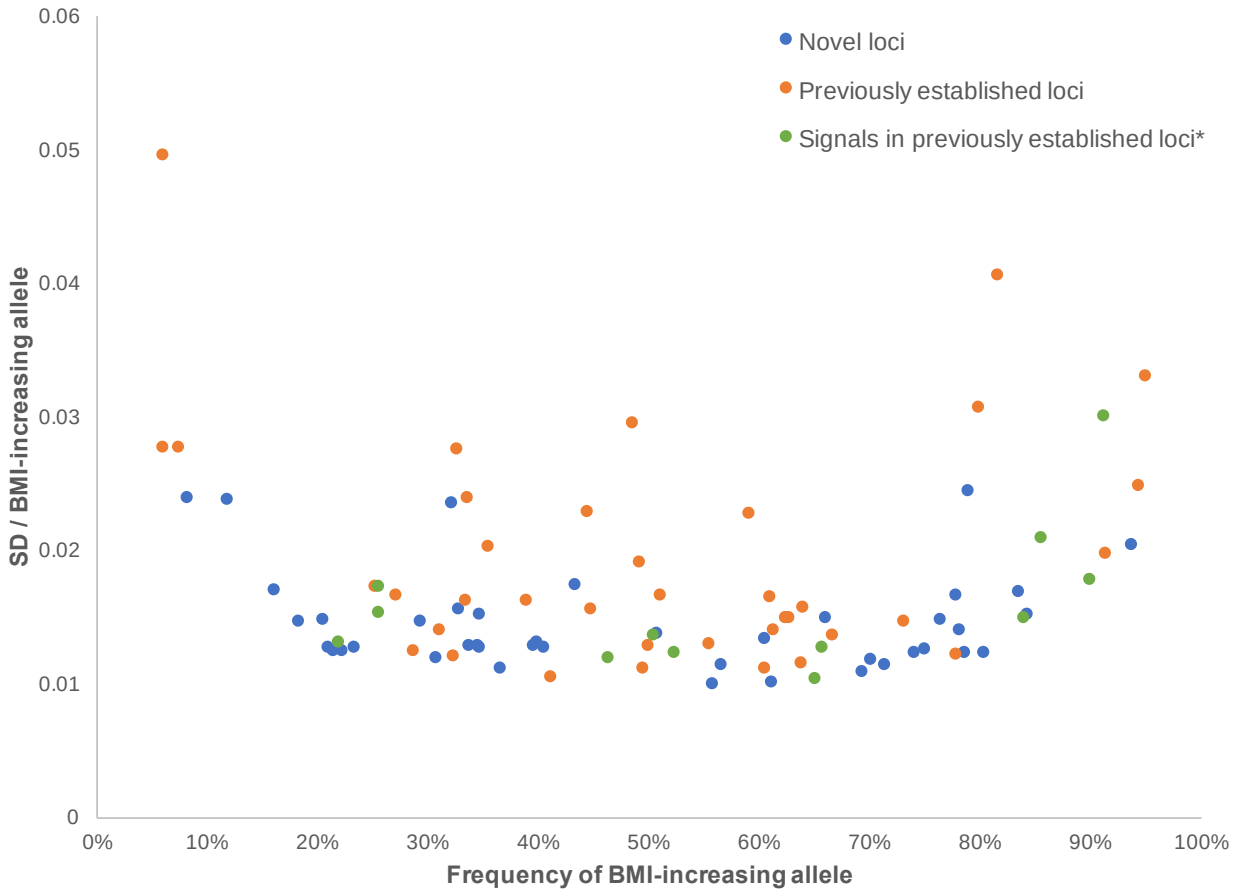




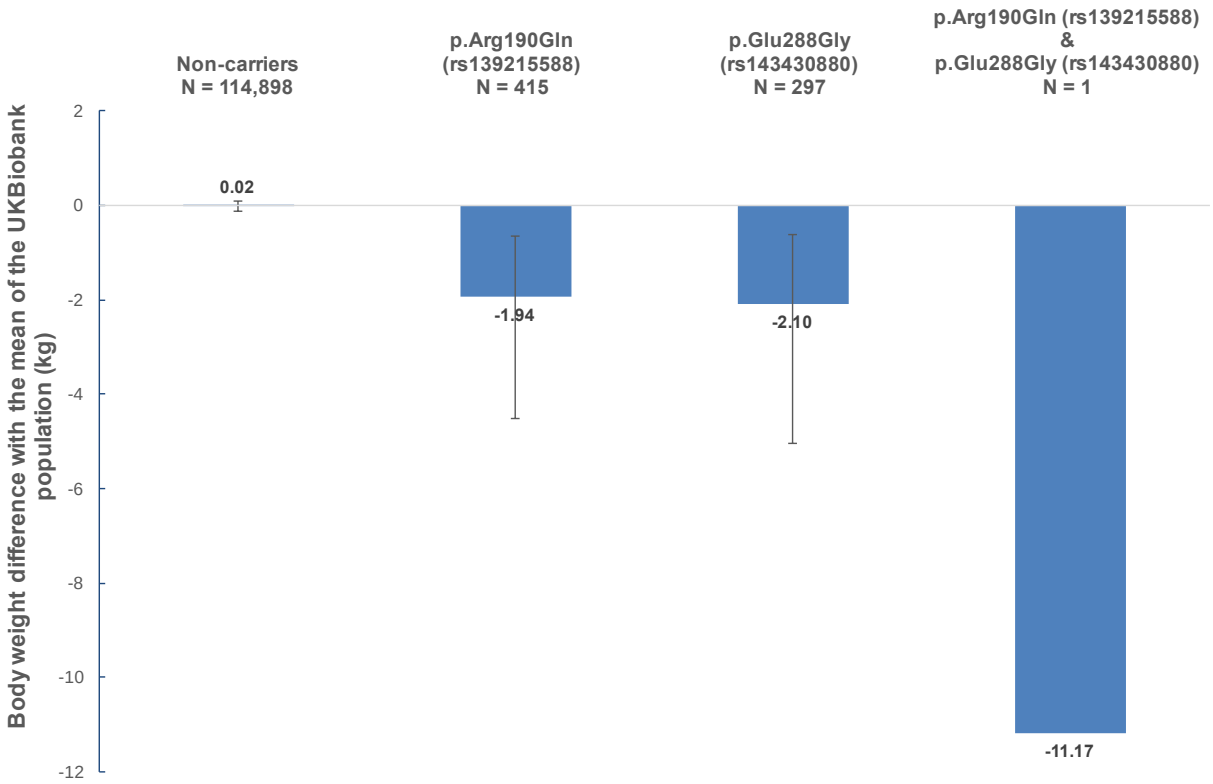




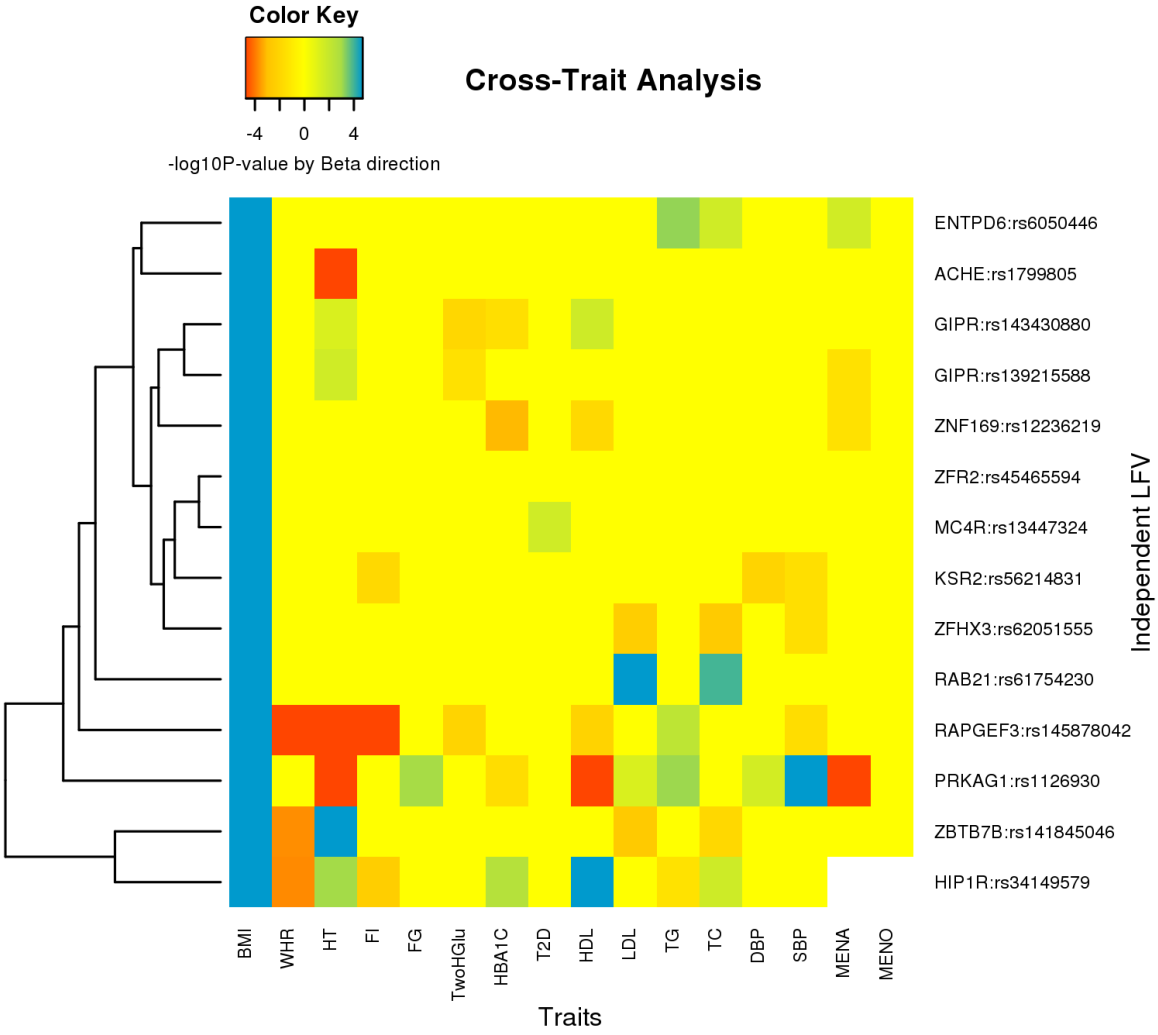
Supplementary Figure 7 | Effect sizes (y-axis) of the 92 common coding variants by their BMI-increasing allele frequency. Effect sizes are expressed in SD per allele (**Supplementary Table 4**). Blue dots represent the 42 novel loci, orange dots represent loci that have been identified before in GWAS for obesity traits, and green dots represent association signals in previously established loci, but for which conditional analyses was not able to convincingly determine the signal as secondary or not (i.e. the previously established lead SNP was not available on the chip).



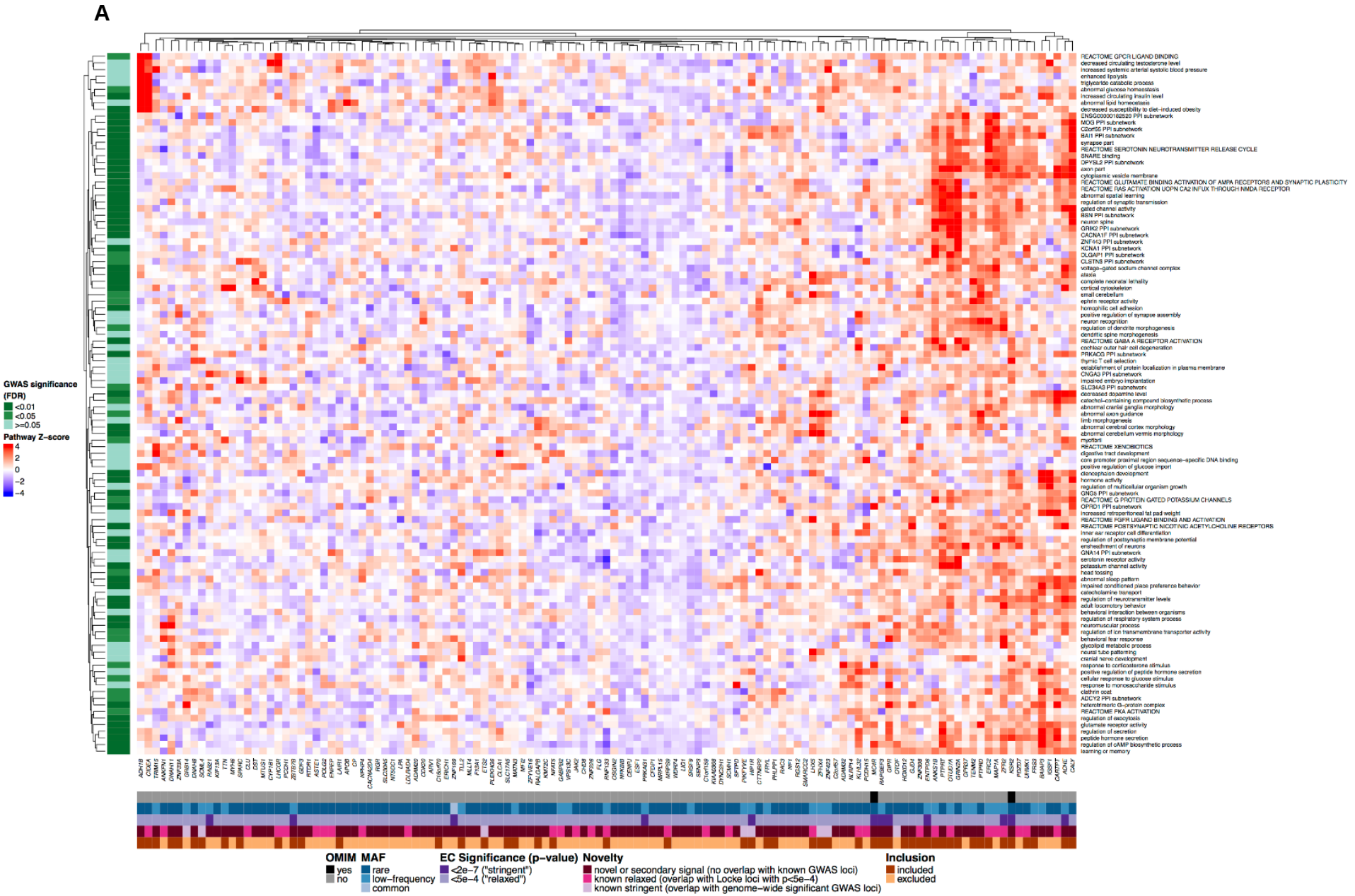
Supplementary Figure 8 | Effects of the two rare SNVs (p.Arg190Gln, p.Glu288Gly) in *GIPR* on BMI in the UK Biobank (N = 115,611, Interim release). Y-axis shows the difference from mean BMI in the UKBiobank, after adjusting for age and sex.

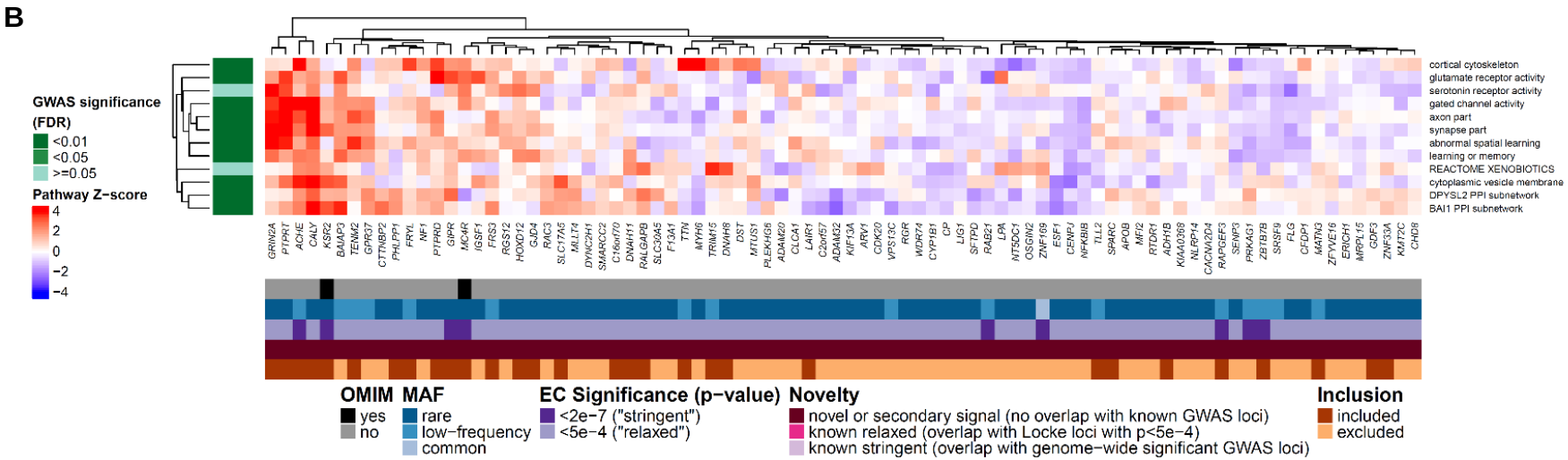


Supplementary Figure 9 | Heatmaps of cross-trait associations for the novel R/LF independent loci identified in the final combined meta-analysis. Heatmap squares are –log10(*P*-values) with red-to-blue shading based on beta effect direction for the BMI-increasing allele in the final combined meta-analysis (blue). Green-to-blue shading hits correspond to positive beta effects with *P*-values between 0.05 and <2E-5, orange-to-red shading hits correspond to negative beta effects with *P*-values between 0.05 to <2E-5, yellow squares are not significant (*P*>0.05), and white squares are missing values. Clustering was done using the complete linkage method with Euclidean distance measure for the loci. SNVs clustering together are more significantly associated with the same set of traits.



Supplementary Figure 10 | Heatmaps showing full DEPICT gene set enrichment results A) of rare and low frequency nonsynonymous SNVs (from main text figure 2), B) of novel rare and low frequency nonsynonymous SNVs, and C) nonsynonymous SNVs of all allele frequencies. For any given square, the color indicates how strongly the corresponding gene (shown on the x-axis) is predicted to belong to the reconstituted gene set (y-axis). This value is based on the gene's z-score for gene set inclusion in DEPICT's reconstituted gene sets, where red indicates a higher and blue a lower z-score. To visually reduce redundancy and increase clarity, we chose one representative "meta-gene set" for each group of highly correlated gene sets based on affinity propagation clustering (**Online Methods, Supplementary Information**). Heatmap intensity and DEPICT *P*-values (see *P*-values in **Supplementary Tables 17-19**) correspond to the most significantly enriched gene set within the meta-gene set. Annotations for the genes indicate (1) whether the gene has an OMIM annotation as underlying a monogenic obesity disorder (black and grey), (2) the minor allele frequency of the significant ExomeChip (EC) variant (shades of blue; if multiple variants, the lowest-frequency variant was kept), (3) whether the variant's *P*-value reached array-wide significance (<2x10-7) or suggestive significance ($<5x10^{-4}$) (shades of purple), (4) whether the variant was novel, overlapping "relaxed" GWAS signals from Locke et al.[3] (GWAS $P<5x10^{-4}$), or overlapping "stringent" GWAS signals (GWAS $P<5x10^{-8}$) (shades of pink), and (5) whether the gene was included in the gene set enrichment analysis or excluded by filters (shades of brown/orange) (**Online Methods and Supplementary Information**). Annotations for the gene sets indicate if the meta-gene set was found significant (shades of green; FDR <0.01, <0.05, or not significant) in the DEPICT analysis of GWAS results from Locke et al.[3]


A
GWAS significance (FDR)
<0.01
<0.05
>=0.05
Pathway Z-score
4
2
0
−2
−4
REACTOME GPCR LIGAND BINDING
decreased circulating testosterone level
increased systemic arterial systolic blood pressure
enhanced lipolysis
triglyceride catabolic process
abnormal glucose homeostasis
increased circulating insulin level
abnormal lipid homeostasis
decreased susceptibility to diet−induced obesity
ENSG00000182520 PPI subnetwork
MOG PPI subnetwork
C2orf16 PPI subnetwork
BAI1 PPI subnetwork
synapse part
REACTOME SEROTONIN NEUROTRANSMITTER RELEASE CYCLE
SNARE binding
DPYSL2 PPI subnetwork
axon part
cytoplasmic vesicle membrane
REACTOME GLUTAMATE BINDING ACTIVATION OF AMPA RECEPTORS AND SYNAPTIC PLASTICITY
REACTOME PAS ACTIVATION UOPN CA2 INFUX THROUGH NMDA RECEPTOR
abnormal spatial learning
regulation of synaptic transmission
gated channel activity
BSN PPI subnetwork
neuron spine
GRIK2 PPI subnetwork
CACNA1F PPI subnetwork
ZNF143 PPI subnetwork
KCNA1 PPI subnetwork
OLGAP1 PPI subnetwork
CLSTN3 PPI subnetwork
voltage−gated sodium channel complex
ataxia
complete neonatal lethality
cortical cytoskeleton
small cerebellum
ephrin receptor activity
homophilic cell adhesion
positive regulation of synapse assembly
neuron recognition
regulation of dendrite morphogenesis
dendritic spine morphogenesis
REACTOME GABA A RECEPTOR ACTIVATION
cochlear outer hair cell degeneration
PRKACG PPI subnetwork
thymic T cell selection
establishment of protein localization in plasma membrane
CNGA3 PPI subnetwork
impaired embryo implantation
SLC34A3 PPI subnetwork
decreased dopamine level
catechol−containing compound biosynthetic process
abnormal cranial ganglia morphology
abnormal axon guidance
limb morphogenesis
abnormal cerebral cortex morphology
abnormal cerebellum vermis morphology
myotonia
REACTOME XENOBIOTICS
digestive tract development
core promoter proximal region sequence−specific DNA binding
positive regulation of glucose import
diencephalon development
hormone activity
regulation of multicellular organism growth
GNGS PPI subnetwork
REACTOME G PROTEIN GATED POTASSIUM CHANNELS
OPRD1 PPI subnetwork
increased retroperitoneal fat pad weight
REACTOME FGFR LIGAND BINDING AND ACTIVATION
REACTOME POSTSYNAPTIC NICOTINIC ACETYLCHOLINE RECEPTORS
inner ear receptor cell differentiation
regulation of postsynaptic membrane potential
ensheathment of neurons
GNA14 PPI subnetwork
serotonin receptor activity
potassium channel activity
head tossing
abnormal sleep pattern
impaired conditioned place preference behavior
catecholamine transport
regulation of neurotransmitter levels
adult locomotory behavior
behavioral interaction between organisms
regulation of respiratory system process
neuromuscular process
regulation of ion transmembrane transporter activity
behavioral fear response
glycolytic metabolic process
neural tube patterning
cranial nerve development
response to corticosterone stimulus
positive regulation of peptide hormone secretion
cellular response to glucose stimulus
response to monosaccharide stimulus
clathrin coat
ADCY2 PPI subnetwork
heterotrimeric G−protein complex
REACTOME PKA ACTIVATION
regulation of exocytosis
glutamate receptor activity
regulation of secretion
peptide hormone secretion
regulation of cAMP biosynthetic process
learning or memory
ADH1B CYP2E1 TSHR AKAP11 ZNF638 DNAH11 DNAH9 SOBP4 RABS1 KCNT2 ITIH MYH6 SPARC CLU DST MTUS1 CYP19A1 LRCH3 RYR3 RTDR1 ADTRP ENPEP LAIR1 APOB CPS1 NPHP4 CACNA2D4 RGR NTNG1 SLC30A5 LPL LOUNAD4 ADAMTS9 CDKN2B ARV1 C16orf70 ENOX1 ZNF184 TLL2 MLLT4 P3SA1 ITGB2 PLEKHG6 CLCA1 SLC17A6 MAP7D3 MYO1E ZFYVE16 RALGAPB KMT2C MYO5B GABPB2 VPS13C JAK2 CASZ1 ZNF638 FLG RNF133 OSGIN2 NOS1AP CENPJ ESR1 PRKAG1 CYLC1 MRPL15 MRPS9 WDR74 LAT1 SIX3 SENP3 C1orf59 KIAA0368 RNF213 SCIMI1 SPTPD PIK3IVE CTTNBP2 FPPL PALLD1 HAO1 NIN RGS12 SMARCC2 LHX3 ZNF804A C2orf57 ZNF483 ADAMTS4 MYO5A KLHL32 PCDH15 MC4R RANGEF3 OTOF HOXD13 GJD4 ZNF536 FAT1 KANK1B PTPRT ITGA2A GRM3 GPR37 TENM2 PTPRD EPB42 MAP1A ZFP2 KSR2 PTPRZ1 UNKL FRS3 BAAP3 KIF1B CACNA1F ACHE CALY
OMIM
yes
no
MAF
rare
low−frequency
common
EC Significance (p−value)
<2e−7 ("stringent")
<5e−4 ("relaxed")
Novelty
novel or secondary signal (no overlap with known GWAS loci)
known relaxed (overlap with Locke loci with p<5e−4)
known stringent (overlap with genome−wide significant GWAS loci)
Inclusion
included
excluded


B
GWAS significance (FDR)
<0.01
<0.05
>=0.05
Pathway Z-score
4
2
0
−2
−4
cortical cytoskeleton
glutamate receptor activity
serotonin receptor activity
gated channel activity
axon part
synapse part
abnormal spatial learning
learning or memory
REACTOME XENOBIOTICS
cytoplasmic vesicle membrane
DPYSL2 PPI subnetwork
BAI1 PPI subnetwork
GRIN2A PTPRT ACHE CALY KSR2 BAIAP3 TENM2 GPR37 CTTNBP2 PHLPP1 FRYL NF1 PTPRD GIPR MC4R IGSF1 FRS3 RGS12 HOXD12 GJD4 RAC3 SLC17A5 MLLT4 DYNC2H1 SMARCC2 C16orf70 DNAH11 RALGAPB SLC30A5 F13A1 TTN MYH6 TRIM15 DNAH8 DST MTUS1 PLEKHG6 ADAM20 CLCA1 LAIR1 C2orf57 ADAM32 KIF13A ARV1 CDK20 VPS13C RGR WDR74 CYP1B1 CP LIG1 SFTPD RAB21 LPA NT5DC1 OSGIN2 ZNF169 ESF1 CENPJ NFKBIB TLL2 SPARC APOB MFI2 RTDR1 ADH1B KIAA0368 NLRP14 CACNA2D4 RAPGEF3 SENP3 PRKAG1 ZBTB7B SRSF9 FLG CFDP1 MATN3 ZFYVE16 ERICH1 MRPL15 GDF3 ZNF33A KMT2C CHD8
OMIM
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MAF
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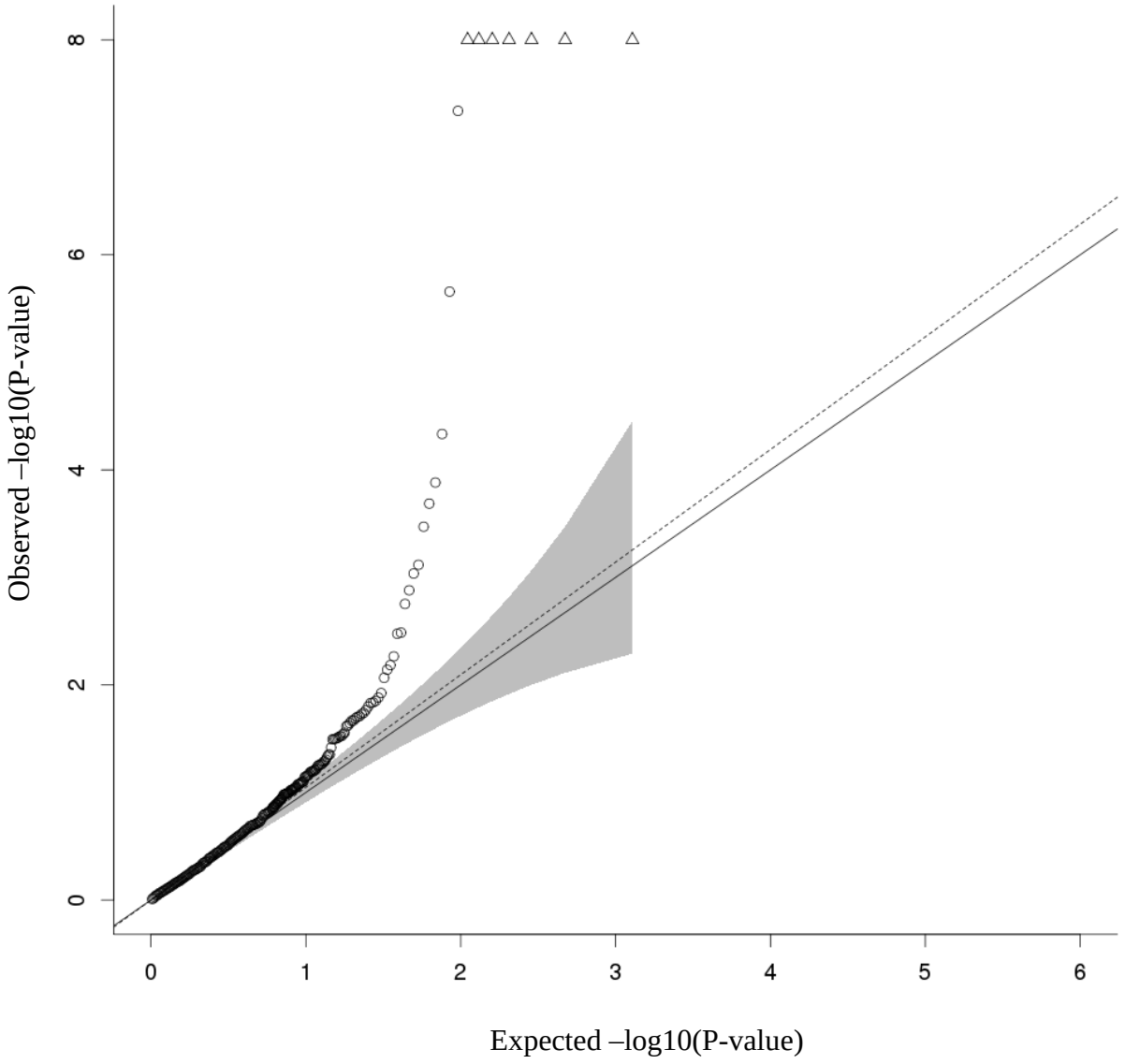
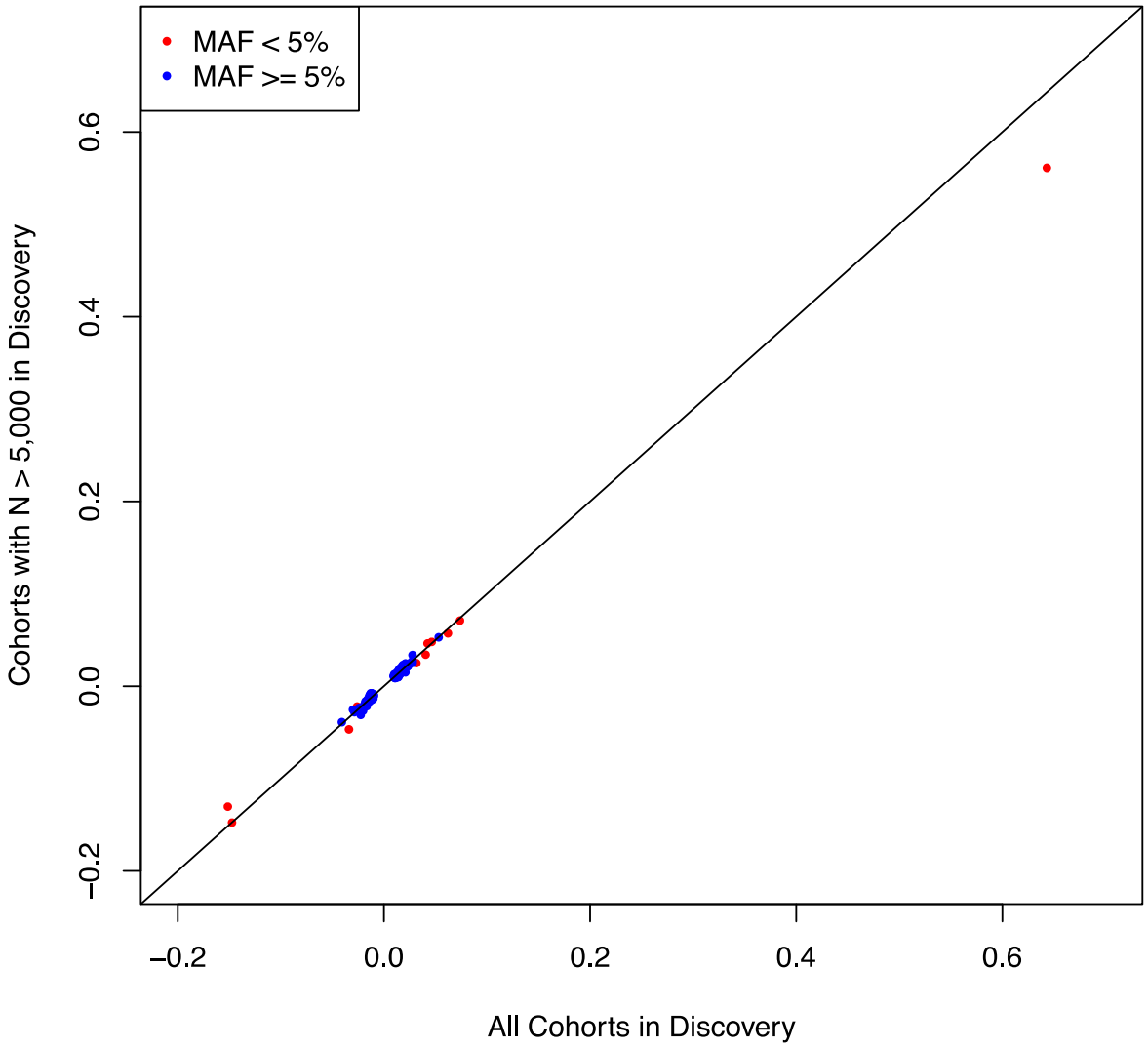
<5e−4 ("relaxed")
Novelty
novel or secondary signal (no overlap with known GWAS loci)
known relaxed (overlap with Locke loci with p<5e−4)
known stringent (overlap with genome−wide significant GWAS loci)
Inclusion
included
excluded
C

Supplementary Figure 11 | Quantile-quantile plot for BMI associations for rare and low-frequency coding SNVs located in monogenic and syndromic genes of obesity. Single variant association results obtained in the final combined meta-analysis are enriched for coding SNVs located in monogenic and syndromic genes of obesity (see gene list and results in **Supplementary Table 21**).



Supplementary Figure 12 | Scatter plot comparison of the effect sizes for all variants that reached significance in the European-ancestry-discovery results (n = 526,508) and results including only studies with sample sizes of more than 5,000 individuals (n = 317,511).

5.



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